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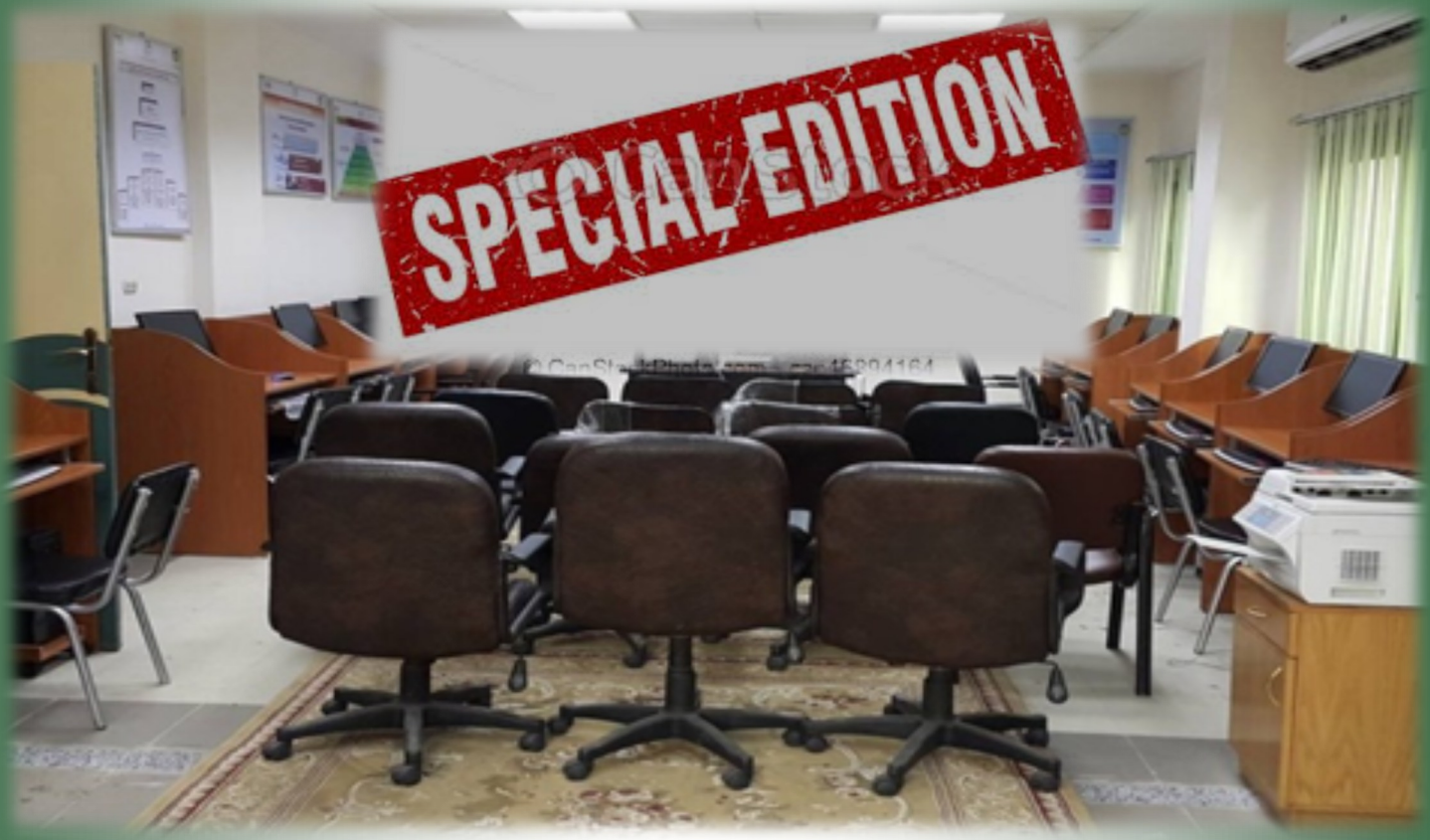
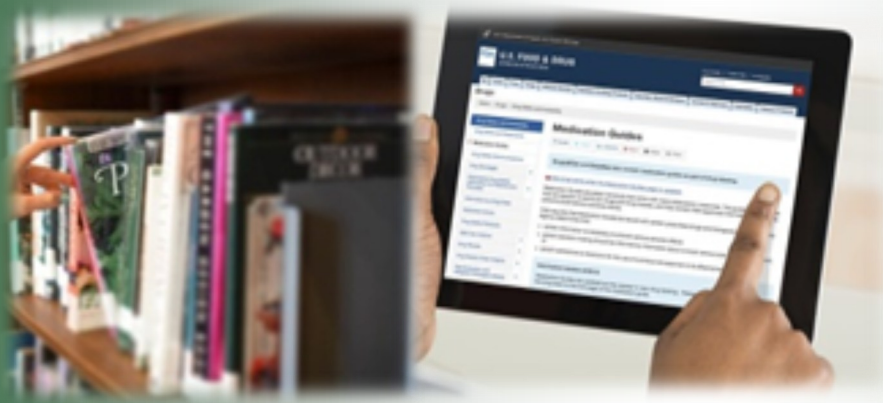
Drug and Poison Information Center Bulletin

Faculty of Pharmacy

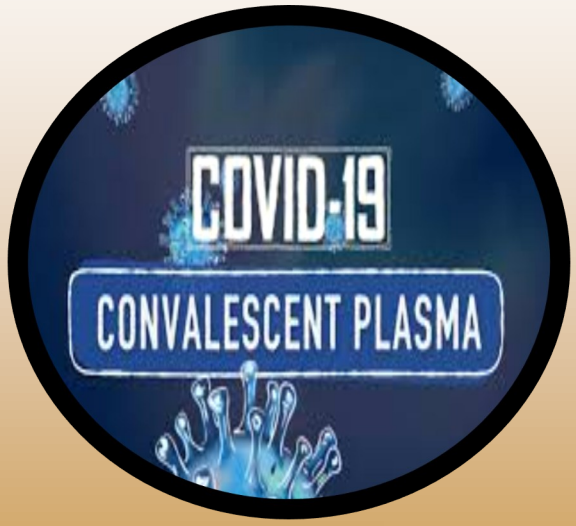
Tanta University

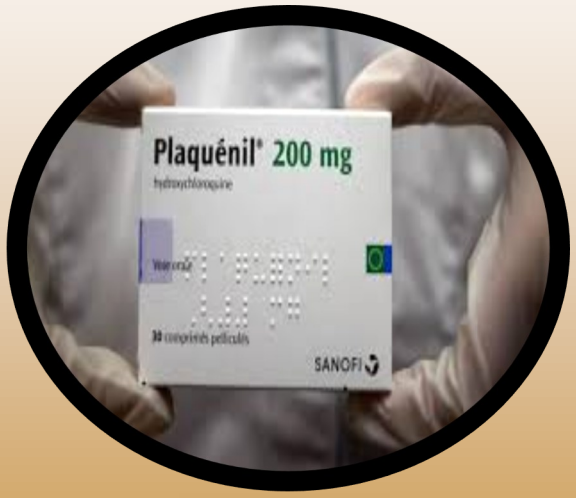




In this special issue

Treatment & prophylaxis options for COVID-19





Hydroxychloroquine (Plaquenil®).....a drug with a lot of controversy

Hydroxychloroquine is an amino-quinoline like chloroquine that granted its Food and Drug Administration (FDA) approval as antimalarial since 1955. It is a commonly prescribed medication in the treatment of uncomplicated malaria, rheumatoid arthritis, and systemic lupus erythematosus.

⇒ Hydroxychloroquine and COVID-19 pandemic:

Since the start of COVID-19 pandemic, chloroquine and hydroxychloroquine were both being investigated for the treatment of severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) infection. Hydroxychloroquine/chloroquine accumulate in human organelles so raise their pH, inhibits antigen processing, and reduces the inflammatory response. They also have immune-modulatory activity by reducing the release of cytokines like interleukin-1 and tumor necrosis factor so theoretically could contribute to an anti-inflammatory response in patients with viral infections. They inhibit glycosylation of angiotensin-converting enzymes (ACE2) receptor so decreases its interaction with the SARS-CoV-2 spike protein, further inhibiting viral entry. Hydroxyl analog of chloroquine has similar mechanisms of action but more favorable dose related toxicity profile than chloroquine. **On February 2020,** China's National Health Commission approved it for the treatment of pneumonia associated with COVID-19. **On 28th of March 2020**, FDA has issued an emergency use authorization for hospitalized adolescent and adult patients with covid-19. **On 24th of April, the FDA** issued a warning against the use of both hydroxychloroquine and chloroquine outside of medical facilities, due to serious and potentially life-threatening heart rhythm complications associated with both drugs.

⇒ Dosing of hydroxychloroquine:

The optimal dosing and duration of treatment for COVID-19 is unknown. The suggested dose in the Emergency Use Authorization (EUA) for hydroxychloroquine sulfate to treat adults and adolescents who: **weigh 50 kg or more and are hospitalized with COVID-19** is 800 mg of hydroxychloroquine sulfate on day 1 then 400 mg daily for 4-7 days of total treatment based on clinical evaluation. According to the Center for Diseases Control and Prevention (CDC), the dose is 400 mg twice daily on day 1, then 200 mg twice daily on days 2-5.

⇒ Monitoring procedures:

A baseline electrocardiogram (ECG), should be obtained to assess for QT interval prolongation and other abnormalities & baseline evaluation of renal and hepatic function.

⇒ Contraindications:

It is contraindicated in the presence of retinal or visual field changes of any etiology. Also, it should not be given to patients with a prolonged QT interval at baseline or at increased risk for arrhythmia.

⇒ Warnings & Precautions:

- **Cardiac effects:** QT interval prolongation. Use with caution in patients with cardiac disease or uncorrected potassium or magnesium and during concomitant administration with QT interval prolonging drugs such as azithromycin. Monitor the ECG during treatment.
- **Severe hypoglycemia:** Hydroxychloroquine sulfate has been reported to decrease insulin clearance and resistance.

- **Hematologic effects:** Pancytopenia, aplastic anemia, and neutropenia have been reported.
- **Central nervous system:** Increases the risk of convulsions and extrapyramidal symptoms.

⇒ **Current situation:**

Despite being one of the most used agents against COVID-19 and its in-vitro activity, hydroxychloroquine is still under investigation to determine its clinical efficacy for treatment or prevention of COVID19 and identify optimal dose and duration and its toxicity profile. Currently (till June 2020) there are more than 200 ongoing research studies on the use of hydroxychloroquine in COVID-19 around the world on **https://clinicaltrials.gov/.** The **RECOVERY** Trial, a large, randomized controlled trial of possible treatments for patients admitted to hospital with COVID-19. Over 11,000 patients have been randomized to investigate various COVID-19 treatment stated on 5 June 2020 that there is no beneficial effect of hydroxychloroquine in patients hospitalized with COVID-19.

References:

- *Yao X, Ye F, Zhang M , et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020 Mar 9.*
- *Fact sheet for health care providers emergency use authorization (EUA) of hydroxychloroquine sulfate supplied from the strategic national stockpile for treatment of COVID-19 in certain hospitalized patients. Available at: (https://www.fda.gov/media/136537/download). Dated 2020 Mar 27. Accessed in April, 2020.*
- *Statement from the Chief Investigators of the Randomised Evaluation of COVid-19 therapy (RECOVERY) Trial on hydroxychloroquine - 5 June 2020. Available at: https://www.recoverytrial.net/ Accessed on 6 June 2020.*

By: Mohammed K. Talaat, PharmD.

Remdesivir, for the treatment of COVID-19

Investigational Antiviral Agent

On May 1, 2020, The U.S. FDA issued the EUA of remdesivir, the broad-spectrum antiviral agent, to allow emergency use of the agent for severe COVID-19 (confirmed or suspected) in hospitalized adults and children. **Severe disease is defined as patients with an oxygen saturation (SpO2) ≤94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO).** EUA for remdesivir was based on preliminary data analysis of the Adaptive COVID-19 Treatment Trial (ACTT) that was announced April 29, 2020. The analysis included 1,063 hospitalized patients with advanced COVID-19 and lung involvement. Preliminary results indicate that patients who received remdesivir had a 31% faster time to recovery than those who received placebo (P< 0.001). Specifically, the median time to recovery was 11 days in patients treated with remdesivir compared with 15 days in those who received placebo. Results also suggested a survival benefit, with a mortality rate of 8% in the remdesivir group, compared with 11.6% in the placebo group, but this was not statistically significant.

⇒ **Mechanism of action:** It has been shown to inhibit the replication of severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003 and Middle East respiratory syndrome coronavirus (MERS -CoV) in 2012.

⇒ **Dosing and administration:** The optimal duration of treatment for COVID-19 is unknown. Under this EUA for remdesivir to treat COVID-19:

The suggested dose for adults, geriatric, and pediatric patients weighing ≥40 kg requiring invasive mechanical ventilation and/or ECMO is a single loading dose of 200 mg infused intravenously on Day 1 followed by once-daily maintenance doses of 100 mg for 9 days (days 2 through 10).
The suggested dose for adults, geriatric, and pediatric patients weighing ≥40 kg not requiring invasive mechanical ventilation and/or ECMO is a single dose of 200 mg infused intravenously on Day 1 followed by once-daily maintenance doses of 100 mg for 4 days (days 2 through 5). If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days.
The suggested dose for pediatric patients with body weight between 3.5 kg and <40 kg requiring invasive mechanical ventilation and/or ECMO is a single loading dose of remdesivir 5 mg/kg IV on Day 1 followed by remdesivir 2.5 mg/kg IV once daily for 9 days (days 2 through 10).
The suggested dose for pediatric patients with body weight between 3.5 kg and <40 kg not requiring invasive mechanical ventilation and/or ECMO is a single loading dose of remdesivir 5 mg/kg IV on Day 1 followed by remdesivir 2.5 mg/kg IV once daily for 4 days (days 2 through 5). If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days.

Pregnancy & breast-feeding considerations: remdesivir should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus. It is not known if remdesivir is present in breast milk. The decision should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother.
Renal impairment: The pharmacokinetics of remdesivir have not been evaluated in patients with renal impairment. Additionally, the excipient sulfobutylether-β- cyclodextrin sodium salt (SBECD) is renally cleared and accumulates in patients with decreased renal function. Adults and pediatric patients (>28 days old**) must have** an estimated glomerular filtration rate (eGFR) determined and full-term neonates (≥7 days to ≤28 days old) must have serum creatinine determined before dosing. Administration of remdesivir is not recommended in adults and pediatric patients (>28 days old) with eGFR less than 30 mL/minute or in full-term neonates (≥7 days and ≤28 days old) with serum creatinine clearance ≥1 mg/dL unless the potential benefit outweighs the potential risk.
Hepatic impairment: The pharmacokinetics of remdesivir have not been evaluated in patients with hepatic impairment. It is not known if dosage adjustment is needed in those patients and remdesivir should only be used in patients with hepatic impairment if the potential benefit outweighs the potential risk. Hepatic laboratory testing **should be** performed in all patients prior to starting remdesivir and daily while receiving remdesivir.
Administer as an IV infusion only over 30 to 120 minutes. Flush line with at least 30 mL normal saline after remdesivir infusion is complete. Do not administer as an intramuscular injection.

⇒ **Contraindications**: Hypersensitivity to remdesivir or any component of the formulation.

⇒ **Warnings & precautions:**

- Hepatic effects: Transaminase elevations have been observed in healthy volunteers and patients with COVID-19. **Do not** initiate remdesivir in patients with alanine aminotransferase (ALT) ≥5 times the the upper limits of normal (ULN) at baseline. Discontinue remdesivir in patients who develop ALT ≥5 times the ULN (may be restarted when ALT is <5 times the ULN) or ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR**.**
- Infusion-related reactions, including diaphoresis, hypotension, nausea, shivering, and vomiting, have been observed during and/or have been temporally associated with remdesivir administration. Discontinue administration and institute appropriate treatment if a clinically significant infusion reaction occurs.
- Use is not recommended in patients with eGFR <30 mL/minute.
- Remdesivir contains the excipient cyclodextrin (sulfobutyl ether beta-cyclodextrin), which may accumulate in patients with kidney impairment.

⇒ **Adverse reactions:** Safety and efficacy have not been yet established. However, increased serum liver enzymes and other infusion related reactions have been observed.

⇒ **Drug interactions:** There are no known significant interactions.

N.B: Safety and effectiveness data of remdesivir use for patients with COVID-19 are still uncertain. Health care providers must submit a report on all medication errors and all serious adverse events related to remdesivir.

References:

- *Treatment of Coronavirus Disease 2019 (COVID-19): Investigational Drugs and Other Therapies. Available at https://emedicine.medscape.com/article/2500116-overview#a3. Updated May 14, 2020. Accessed May 16, 2020.*
- *FDA. Coronavirus (COVID-19) Update: FDA Issues Emergency Use Authorization for Potential COVID-19 Treatment. fda.gov. Available at https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment. Published May 1, 2020. Accessed May 16, 2020.*
- *FDA. FACT SHEET FOR HEALTH CARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) of remedesvir (GS-5734™). fda.gov. Available at https://www.fda.gov/media/137566/download. Published May 1, 2020. Accessed May 16, 2020.*
- *Remdesivir drug monograph. Available at https://online.lexi.com/lco/action/doc/retrieve/docid/multinat_f/6925337?cesid=3YXy27d9trb&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dremdesivir%26t%3Dname%26va%3Dremdesivir. Accessed May 16, 2020.*

By: Bassant Maher, M.Sc.

Favipiravir (Avigan)® for treatment of COVID-19

Approved, investigational antiviral

⇒ Description:

Favipiravir is a modified pyrazine analog that was initially approved for therapeutic use in resistant cases of influenza. It targets RNA-dependent RNA polymerase (RdRp) enzymes, which are necessary for the transcription and replication of viral genomes. Favipiravir inhibits replication of influenza A and B, and has shown promise in the treatment of avian influenza, and may be an alternative option for influenza strains that are resistant to neuramidase inhibitors.

⇒ **Classification**: It acts as a substrate and inhibitor for different enzymes and transporters in the cells as in the following table:

Cytochrome P-450-2CB Inhibitor	**Experimental un-approved treatment for COVID-19**	**Organic Anion Transporter-1 (OAT1/SLC22A6) inhibitor**
Cytochrome P-450 2E1 Inhibitor	**P-glycoprotein inhibitor**	**Organic Anion Transporter-1 (OAT1/SLC22A8) inhibitor**

⇒ Indications:

In 2014, avipiravir was approved in Japan to treat cases of influenza that were resistant to conventional treatment. Given its efficacy at targeting several strains of influenza, it has been investigated in other countries to treat novel viruses including Ebola and most recently, COVID-19.

⇒ Mechanism of action:

It is a prodrug and undergoes ribosylation and phosphorylation intra-cellularly to become the active favipiravir-RTP. Favipiravir-RTP binds to and selectively inhibits RNA dependent RNA polymerase (RdRp), which ultimately prevents viral transcription and replication. Some studies have shown that when favipiravir-RTP is incorporated into a growing RNA strand, it prevents RNA strand elongation and viral proliferation. Studies have also found that the presence of purine analogs can reduce favipiravir's antiviral activity, suggesting competition between favipiravir-RTP and purine nucleosides for RdRp binding.

⇒ Pharmacokinetics:

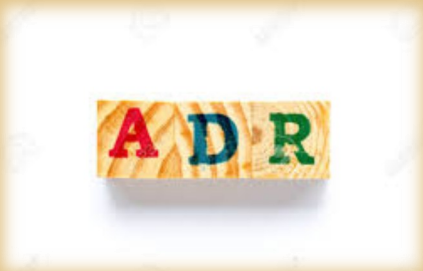
Absorption	**The bioavailability of favipiravir is almost complete at 97.6%. The mean Cmax for the recommended dosing schedule of favipiravir is 51.5 ug/mL.**
Distribution	The apparent volume of distribution is 15 - 20 L. Favipiravir is 54% plasma protein-bound. Of this fraction, 65% is bound to serum albumin and 6.5% is bound to α1-acid glycoprotein.
Metabolism	Favipiravir is extensively metabolized with metabolites excreted mainly in the urine. The antiviral undergoes hydroxylation primarily by aldehyde oxidase and to a lesser extent by xanthine oxidase to the inactive metabolite, T705M1.
Excretion	Favipiravir's metabolites are predominantly renally cleared.

⇒ Dosage and Administration:

The usual dosage of favipiravir for adults is 1600 mg orally twice daily for 1 day followed by 600 mg orally twice daily for 4 days. The total administration period should be 5 days.

⇒ Adverse effects:

In Japanese clinical studies and the global phase III study (studies conducted with dose levels lower than the approved dosage), adverse reactions were observed in 100 of 501 subjects (19.96%) evaluated for the safety (including abnormal laboratory test values). Major adverse reactions included:



- Increase of blood uric acid level in 24 subjects (4.79%).
- Diarrhoea in 24 subjects (4.79%).
- Decrease of neutrophil count in 9 subjects (1.80%).
- Increase of Aspartate aminotransferase (AST/sGOT) in 9 subjects (1.80%), increase of Alanine aminotransferase (ALT/ (sGPT) in 8 subjects (1.60%).

⇒ Contraindications:

- Women known or suspected to be pregnant as teratogenic effects occurred in animal studies.
- Patients with hypersensitivity to any ingredients of the drug.

⇒ Warnings & precautions:

- Avigan® is a drug the use of which is considered only when there is an outbreak of novel or re-emerging influenza virus infection in which other anti-virals are ineffective and the government decided to use it as a countermeasure against such influenza viruses.
- It should be administered only according to government directions and to the appropriate patients.
- It is not effective against bacterial infections.

⇒ References:

- *Favipiravir-Complete Monograph. Available at: https://www.drugbank.ca/drugs/DB12466#reference-A191961. Accessed in April, 2020.*
- *Avigan Pamphlet. Available at: Medical Information Center, Taisho Toyama Pharmaceutical Co., Ltd. And TOYAMA CHEMICAL CO., LTD.*

By: Marwa EL-Sayed, PGCPD.

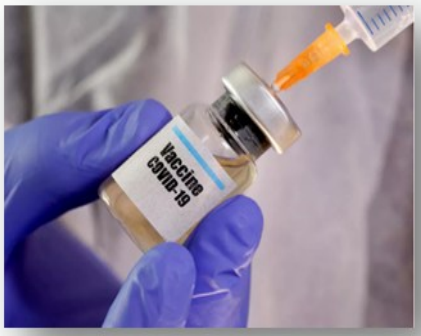
Convalescent plasma for the treatment of COVID-19

- Convalescent plasma refers to antibody-rich products that are collected from eligible recovered donors.
- The use of convalescent plasma has a long history in the treatment of infectious diseases, proposed using it as a treatment for COVID-19.
- Convalescent plasma has not yet been shown to be effective in COVID-19.
- The FDA states that it is important to determine its safety and efficacy via clinical trials before routinely administering convalescent plasma to patients with COVID-19.
- To date, two small case series have been published. These series reported improvement in oxygenation, sequential organ failure assessment (SOFA) scores, and eventual ventilator weaning in some patients. The timelines of improvement varied from days to weeks. Caution is advised, as these were not controlled trials and other pharmacologic methods (antivirals) were used in some patients.

References: :Treatment of Coronavirus Disease 2019 (COVID-19): Investigational Drugs and Other Therapies. Available at https://emedicine.medscape.com/article/2500116-overview#a3. Updated May 14, 2020. Accessed on May 16, 2020.

By: Bassant Maher, M.Sc.

Promising vaccines against COVID-19



Less than five months after the world first learned about the new coronavirus causing fatal pneumonia in Wuhan, China, there are more than 90 vaccines for the virus at various stages of development, with more announced each week. Now, developers, funders, and other stakeholders are laying the groundwork for their biggest challenge yet: determining which vaccines work.

This typically involves giving thousands or tens of thousands of people a vaccine or placebo and seeing, over months or even years, whether there is a difference between the two groups in how many people get infected in the course of their daily lives, as well as checking that no safety issues emerge.

Investigational Vaccines for COVID-19

⇒ **ChAdOx1 nCoV-19 vaccine (Jenner Institute, Oxford University; AstraZeneca):** Genetic material is used to make proteins from the COVID-19 virus (SARS-CoV-2) called Spike glycoprotein (S). This protein is usually found on the surface of SARS-CoV-2 and plays an essential role in the infection pathway of the SARS-CoV-2 virus. The SARS-CoV-2 coronavirus uses its spike protein to bind to ACE2 receptors on human cells to gain entry to the cells and cause infection has been added to the ChAdOx1 construct, that is made from a virus (ChAdOx1), which is a weakened version of a common cold virus (adenovirus) that causes infections in chimpanzees, that has been genetically changed so that it can't grow in humans. In total, this study will enroll up to 10,260 adults and children across the UK. The phase II part of the study involves expanding the age range of people the vaccine is assessed in, to include a small number of adults and children divided into 3 age groups as follow:

- **56-69 years old.**
- **Over 70 years old.**
- **Ages between 5-12 years.**

For these groups, researchers are assessing the immune response to the vaccine in people of different ages, to find out if there is variation in how well the immune system responds in older people or children. The phase III part of the study involves assessing how the vaccine works in a large number of people over the age of 18. This group will allow assessment of how well the vaccine works to prevent people from becoming infected with COVID-19.

⇒ **China CpG 1018 adjuvant (Dynavax) and Sinovac's,** Collaboration for the adjuvanted vaccine that will combine Dynavax's CpG 1018, the adjuvant contained in the U.S. FDA-approved HEPLISAV-B vaccine, with Sinovac's chemically inactivated coronavirus vaccine candidate. The company secured approval in April to conduct Phase I/II clinical trials of the vaccine candidate in China. It has begun the Phase I trial in 144 healthy adult participants aged 18-59 years. During the Phase I study, CoronaVac's safety, tolerance, and preliminary immunogenicity were evaluated. Following preliminary evidence of the safety profile of the vaccine in the Phase I trial, a Phase II study was commenced for assessment of the vaccine's immunogenicity and safety in a larger population to determine dosage, regimen, and immunization schedule. The company is establishing a commercial vaccine production plant to manufacture up to 100 million doses of CoronaVac per year.

⇒ **mRNA vaccine BNT162 (BioNTech and Pfizer),** The first participants have been dosed in the U.S. in the Phase 1/2 clinical trial for the BNT162 vaccine program to prevent COVID-19. The trial is part of a global development program, and the dosing of the first cohort in Germany was completed. The Phase 1/2 study is designed to determine the safety, immunogenicity, and optimal dose level of four mRNA vaccine candidates evaluated in a single, continuous study. The dose level escalation portion (Stage 1) of the Phase 1/2 trial in the U.S. will enroll up to 360 healthy subjects into two age cohorts (18-55 and 65-85 years of age). The first subjects immunized in Stage 1 of the study will be healthy adults 18-55 years of age. Older adults will only be immunized with a given dose level of a vaccine candidate once testing of that candidate and dose level in younger adults has provided initial evidence of safety and immunogenicity.

⇒ **Adjuvanted vaccine (GlaxoSmithKline and Sanofi);** Sanofi will contribute its S-protein COVID-19 antigen, which is based on recombinant DNA technology. This technology has produced an exact genetic match to proteins found on the surface of the virus, and the DNA sequence encoding this antigen has been combined into the DNA of the baculovirus expression platform. The use of an adjuvant can be added to some vaccines to enhance the immune response and has been shown to create a stronger and longer-lasting immunity against infections than the vaccine alone. The companies plan to initiate phase I clinical trials in the second half of 2020.

References:

- *Phase II/III Trial Explained | COVID-19. Available at: https://covid19vaccinetrial.co.uk/phase-iiiii-trial-explained. Accessed in June, 2020.*
- *Dynavax and Clover Biopharmaceuticals Announce Research Collaboration to Evaluate Coronavirus (COVID-19) Vaccine Candidate with CpG 1018 Adjuvant | Dynavax Technologies Corporation. Available at:http:// investors.dynavax.com/news-releases/news-release-details/dynavax-and-clover biopharmaceuticals-announce-research. Accessed in May, 2020.*
- *Pfizer and BioNTech Dose First Participants in the U.S. as Part of Global COVID-19 mRNA Vaccine Development Program | Pfizer. Available at: https://www.pfizer.com/news/press-release/press-release-detail/pfiz-er_and_biontech_dose_first_participants_in_the_u_s_as_part_of_global_covid_19_mrna_vaccine_development_program. Accessed in May, 2020.*
- *Sanofi and GSK to join forces in unprecedented vaccine collaboration to fight COVID-19 | GSK.Available at: https://www.gsk.com/en-gb/media/press-releases/sanofi-and-gsk-to-join-forces-in-unprecedented-vaccine-collaboration-to-fight-covid-19/. Accessed in May, 2020.*

By: Mai Mousa, PharmD

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