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Immunogenicity induced by COVID-19 vaccines in Mexican population: mRNA expression for IgG anti-spike.

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Introduction:

In December 2019, health authorities in Wuhan, Hubei province, China issued an epidemiological alert for an outbreak of pneumonia of unknown causes, the infected patients had in common having visited a local seafood and wild animal market[1].

At the beginning of the outbreak, samples from seven patients with severe pneumonia in the intensive care unit (ICU) of Wuhan Jin-Yin-Tan Hospital were obtained for analysis by the Wuhan Institute of Virology (WIV) to isolate the pathogen causing the disease. After studying the samples received, the WIV identified a new coronavirus as responsible for the outbreak, which shares 79.6% similarity to the genomic sequences of SARS-CoV and 96% similarity to those of a bat coronavirus.[2,3] Based on the phylogenetic and taxonomic characteristics of the virus, the International Committee on Taxonomy of Viruses officially named the newly detected virus; severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2)[4] and the disease caused by this virus has been termed; Coronavirus disease 2019 (COVID-19), an extremely contagious respiratory infection.[5]

In an attempt to contain the epidemic, the Chinese government took a series of measures to prevent the displacement of millions of people inside and outside the country; however, many of them have already left the country to go on vacation to other places to celebrate the traditional Chinese New Year.[6] On January 30, 2020, the World Health Organization (WHO) announced that the SARS-CoV-2 pneumonia outbreak was a global health emergency[7] and on March 11 declared the disease COVID-19 a pandemic.[8] As of August 26, 2021, 213,752,662 confirmed cases and 4,459,381 deaths have been reported worldwide; in Mexico, 3,291,761 total cases and 256,287 total deaths due to COVID-19 have been reported.[9] For this reason, the WHO has created a database containing the results of research on COVID-19

conducted by scientists and health professionals from around the world, which has allowed accelerating the processes of diagnosis, treatment and vaccine development.[10]

According to the information provided by WHO, it is vital to continue research to answer a number of questions about the vaccines currently in use, which have been licensed for emergency use to combat the COVID-19 pandemic. One of the most worrisome questions concerns the duration of the immunity conferred by these vaccines and, moreover, whether they will protect the population from the new SARS-CoV-2 strains that continue to appear.

General description of coronaviruses

Coronaviruses (CoVs) belong to the Coronaviridae family and consist of an envelope and a single strand of positive-sense, non-segmented ribonucleic acid (RNA). The genomic organization of all CoVs is similar; the non-structural proteins are encoded within the two thirds of the 5' end and the structural proteins called; spike (S), envelope (E), membrane (M) and nucleocapsid (N) are encoded in the 3' third.5,[11] The name coronavirus is due to the characteristic crown-like appearance of the virions, this morphology is given by the spike-shaped proteins embedded in the envelope.[12] Based on their phylogenetic properties, CoVs are divided into four genera; group 1 (alpha-CoV), group 2 (beta-CoV), group 3 (gamma-CoV), group 4 (delta-CoV).[13]

This family of viruses has been known since the 1930s, they were identified as pathogens responsible for infectious diseases in farm animals, and they are also responsible for diseases in a wide variety of animals including humans.[14]

Before SARS-CoV-2 appeared, six species of coronaviruses were already known to cause disease in humans, four of which cause mild symptoms of the common cold in non-immunocompromised individuals. The other two strains are of zoonotic origin;

SARS-CoV, responsible for outbreaks of severe respiratory syndrome in 2002 and 2003, and MERS-CoV, which caused severe respiratory illness in the Middle East in 2012.[15]

Genomic structure of SARS-COV-2

The structural proteins of SARS-CoV-2 play a key role in the interaction of the virus with host cells. The S protein consists of two subunits, S1 and S2. The S1 subunit contains the receptor binding domain (RBD) that binds to the host cell receptor, while the S2 subunit facilitates fusion of the viral envelope with the cell membrane. Angiotensin converting enzyme type 2 (ACE-2) has been identified as the main receptor for SARS-CoV-2, this receptor is predominantly expressed on type II pneumocytes, airway epithelium, digestive tract, endothelium, kidney, fibroblasts, and various immune cells.[16-19] The M protein confers structure to the virus, once bound to the nucleocapsid it regulates virus assembly, and also contains T-cell epitopes that trigger the production of neutralizing antibodies in infected individuals. The E protein is essential for the assembly, release and pathogenesis of the virus. The N protein is key in the formation of complexes with the viral genome, enhances the functions of the M protein and increases viral replication.[20]

COVID-19

COVID-19 is defined as the disease caused by the new SARS-CoV-2 coronavirus. The main mechanism of transmission is by the airborne route through contact with flung droplets and aerosols that are released by an infected person when talking, coughing or sneezing, especially in crowded, closed and poorly ventilated places.[21-25] Other means of spreading the virus are: contact with objects or surfaces containing the virus, constant touching of the face (eyes, nose or mouth) as well as shaking hands with an infected person.[26]

The incubation period varies between 5 and 7 days. The clinical presentation is not specific; it can range from asymptomatic to extremely severe. The most common symptoms are fever, nonproductive cough, muscle pain, fatigue and dyspnea; some patients may also present with headache, nausea and diarrhea, especially early in the course of infection, prior to the onset of fever. Recent studies indicate that the severity of the disease correlates with age (> 60 years) and with the presence of underlying diseases (hypertension, diabetes, heart disease); these groups of patients are at higher risk of developing acute respiratory distress, pneumonia and even death.[22,27,28] Several tests are currently available for the diagnosis of COVID-19, but the reverse transcriptase polymerase chain reaction (rt-PCR) test is the gold standard diagnostic technique.[29,30]

Vaccines and COVID-19

To date, there is no specific treatment for COVID-19.[31] For this reason, efforts have focused on preventing the spread of the disease through mitigation measures and on seeking herd immunity, also known as flock immunity, through vaccination.[32,33] Research conducted after the SARS-CoV epidemic in 2003 has laid the groundwork for the development of vaccines against COVID-19, due to the genetic similarity shared by both CoVs.[34]

Historically, the implementation of vaccination programs, especially during childhood, has been the key to controlling and/or eradicating countless infectious and contagious diseases. Vaccines prepare the immune system to create immunoglobulins that can later recognize the pathogen in question and attack it, thus breaking the chain of disease transmission.[35,36]

As of June 3, 2021, WHO has assessed that the following COVID-19 vaccines meet the criteria of safety and efficacy for population use.[37]

Based on viral vectors

- Oxford/AstraZeneca (ChAdOx1 nCoV-19)

It is a vaccine that uses the chimpanzee adenovirus ChAdOx1 as a vector, expressing the S protein of SARS-CoV-2. According to data provided by the WHO and other studies, the vaccine has an efficacy of 63.09% against symptomatic SARS-CoV-2 infection. It is recommended to apply two doses of 0.5 ml each by intramuscular route with an interval of 8 to 12 weeks. It was authorized by the Federal Commission for Protection against Sanitary Risks (COFEPRIS) on January 4, 2021 for use in Mexico.[38-41]

- Janssen (Ad26.COV2-S)

This is a single-dose vaccine using a non-replicating adenoviral vector of serotype 26 containing the S protein of SARS-CoV-2. Phase 3 results published by Johnson&Johnson Pharmaceuticals indicate that the efficacy of the Janssen vaccine against moderate to severe COVID-19 infection was 72% in the United States of America, 66% in Latin America and 57% in South Africa 28 days after inoculation. The WHO Strategic Advisory Group of Experts (SAGE) recommends a dose of 0.5 ml administered intramuscularly. COFEPRIS authorized its use in Mexico on May 27, 2021.[41-44]

Based on nucleic acids

- Pfizer BioNTech (BNT162b2)

This vaccine contains the mRNA coding for the S protein of SARS-CoV-2. According to the results of a multinational trial to assess the efficacy and safety of BNT162b2, it was concluded that after administration of two doses of 0.3 ml respectively 21 days apart, the efficacy was 95% against symptomatic infection caused by SARS-CoV-2 in persons older than 16 years of age. WHO recommends administering two doses 21 to 28 days apart, COFEPRIS authorized its use in Mexico on December 11, 2020.[41, 45, 46]

- Modern (mRNA-1273)

Like the previous one, it contains the mRNA encoding the S protein of SARS-COV-2 encapsulated in lipid nanoparticles. Phase 3 trials for the mRNA-1273 vaccine showed 94.1% efficacy in preventing severe COVID-19 infection that can be observed after day 14 of the first application. WHO recommends the use of two doses of 0.5 ml each with an interval of 28 days. In Mexico, its use was authorized by COFEPRIS on August 17, 2021.[41,47,48]

Based on inactivated viruses

- Sinovac (CoronaVac)

It is a vaccine formulated based on incubation of SARS-CoV-2 (CN02 strain) in Vero cells. A Phase 3 trial conducted in Turkey tested the efficacy and safety of this vaccine in volunteers between 18 and 59 years of age. The double-blind, randomized, placebo-controlled study concluded that the vaccine confers good humoral response against SARS-CoV-2, as well as high efficacy against symptomatic COVID-19 confirmed by PCR. It reports 51% efficacy against SARS-CoV-2 infection, 100% efficacy against severe infection and 100% efficacy against hospitalization from day 14 after receiving the second dose. The SAGE recommends applying two doses of 0.5 ml intramuscularly with a separation of 2 to 4 weeks between the first and second dose. In Mexico, COFEPRIS authorized its use as of February 9, 2021.[41,49,50]

- Sinopharm (COVID-19 inactivated vaccine, Vero cells)

It uses the same inactivation process as Sinovac but using the HB02 strain of SARS-CoV-2. A multi-country Phase 3 trial demonstrated 79% efficacy against symptomatic SARS-CoV-2 infection 14 days after the second dose. WHO recommends the application of 2 doses of 0.5 ml respectively, with a separation of 3 to 4 weeks between the first and second dose. It was recently approved by COFEPRIS on August 25, 2021 for use in Mexico.[41, 51, 52]

Justification

Currently, the pandemic originated by COVID-19 continues to be a serious public health problem in our country (Mexico) that implies a great investment by the federal government to combat the ravages caused by it, so it is of vital importance to determine the explicit mechanisms by which the different vaccines administered in our population have their protective effects on the virus infection. Therefore, this study focuses on identifying the molecular mechanisms by which inhibitions of virus recognition by the human host cell are carried out.

Problem Statement

The precise mechanism by which a vaccinated patient has a high probability of being infected with a different strain of SARS-CoV-2 is currently unknown. Assuming this, recontagion and further increases in the rates of active cases of COVID-19 in the vaccinated population are not prevented. Therefore, by determining the molecular mechanisms of infection, therapeutic targets can be identified, and specific treatments can be offered to prevent infection in both first-contact subjects and those with a history of COVID-19 infection.

Hypothesis

Gene expression for IgG anti-spike in subjects with a complete vaccination schedule against COVID-19 does not develop the necessary immunogenicity in the Mexican population to prevent re-contagion.

General Objective

To characterize the immunogenicity induced by COVID-19 vaccines in Mexican population: mRNA expression for IgG anti-spike.

Specific objectives

1. Determine the mechanisms of virus transmission on the cell.
2. To identify the study population.
3.To identify the anti-spike IgG genes in vaccinated population.

Methodology

Type of study, general design and population

A quasi-experimental, longitudinal, retrolective, comparative, quasi-experimental study will be carried out in a Mexican population older than 18 years with a complete vaccination schedule against COVID-19, to determine the immunogenicity induced by the vaccines.

Four study groups will be formed.

- Group 1: 20 persons who have received the Oxford/AstraZeneca vaccine (ChAdOx1 nCoV-19).
- Group 2: 20 persons who received the Gamaleya National Center vaccine (Sputnik V).
- Group 3: 20 people who have received the Pfizer/BioNTech vaccine (BNT162b2)
- Group 4: 20 persons who have received Sinovac vaccine (CoronaVac)

Inclusion criteria:

1.- Persons of Mexican origin.
2.- Over 18 years of age.
3.- With complete vaccination schedule against COVID-19.
4.- Allowing peripheral blood samples to be taken.
5.- To sign an informed consent form.
6.-Who agree to participate in the protocol.

Exclusion criteria:

1.- Persons with incomplete vaccination schedule against COVID-19.

Persons who have 30 +/- 5 days after having completed the COVID-19 vaccination schedule.

3.- People under treatment with any immunosuppressive drug.

4.- Persons who refuse to sign the informed consent.

Elimination criteria:

1.- Subjects who during the study develop COVID-19.

2.- Subjects who decide to leave the study before the stipulated time for the collection of the required blood samples.

Procedure:

(a) Participants were selected by clinical history to assess current health status, obtain demographic data, as well as personal pathological history of importance for the study (chronic degenerative diseases, history of COVID-19 disease).

b) Peripheral venous blood samples (3 ml per occasion) will be taken from all participants. They will be carried out on days 30,60 and 120 after completion of the COVID-19 vaccination schedule.

c) Sample processing:

tRNA extraction from all samples.

cDNA synthesis

Real time PCR performance.

Ethical Aspects

The present study will strictly follow the ethical norms for research established in the Declaration of Helsinki, at the international level. This Declaration suggests that the sole purpose of research in humans should be the improvement of diagnostic, therapeutic and prophylactic methods, as well as the understanding of the etiology and pathogenesis of diseases. At the national level, according to article 17 of the Regulations of the General Health Law on Health Research, this study is considered of minimal risk for the participants, since 3mL of blood will be taken by venous

puncture. Individuals who wish to participate will be asked to sign the specific informed consent form, after a thorough explanation of the procedure.

The data obtained from the individuals participating in the study will be protected by the “Federal Law for the protection of personal data”, so the anonymity of the samples and the participants is guaranteed. The results of the study will be under the custody and responsibility of the principal investigator for subsequent analysis and publication in scientific journals.

Schedule		
Stage 1	Stage 2	Stage 3
Sample collection	Experimental	Analysis of results and re writing.
Duration: 4 months (Septeml December 2021)	Duration: 4 months (January-/ 2022)	Duration: 3 months (May- 2022)
Collection and transport of bl samples from all selec participants.	✓ Extraction of tRNA from bl samples. ✓ cDNA synthesis. ✓ Real-time PCR.	

Statistical analysis

Descriptive phase: The results were presented in tables for continuous variables with normal distribution in measurements ± standard deviation and for free distribution in medians and percentiles. While the categorical variables were presented in percentages and total figures.

Bivariate phase: To look for differences in the quantitative variables according to the Kolmogorov-Smirnov normality test, the student t test or the Mann-Whitney U test were used or for the related ordinal variables the Wilcoxon test. The dichotomous or ordinal related qualitative variables were analyzed with the McNemar test, for the dichotomous or ordinal variables not related they were analyzed with the chi square test or Fisher's exact test.

Multivariate phase: To compare and find the differences in more than two groups in the quantitative variables with free distribution the Kruskall-Wallis test; for the related samples with free distribution the Friedman test was used. All calculations were performed using the current version of the SPSS statistical package for Windows and the Jamovi program version 4.1 of R. Statistical significance was considered to be a P value <0.05 and a confidence interval of 95%.

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