

Safety and immunogenicity of vaccines against SARS-CoV-2

Seguridad e inmunogenicidad de vacunas contra SARS-CoV-2

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Abstract

The mortality rate estimated by the WHO worldwide for COVID-19 has been 5.7%, much higher than other communicable infectious diseases, so it is essential to apply a vaccine to the population to reduce the viral spread, according to the WHO there are 23 projects in clinical phase stage III, such as vaccines: ChadOx1, nCov-19, Gam-COVID-Vac, CoronaVac that show promising results in research published by The Lancet Infection Diseases journal, for which we consider correlating the three vaccines and determining which is safer, generates greater immunogenicity and less reactogenicity in volunteer participants, for which we conducted a review bibliography and a meta-analysis of high impact scientific articles, concluding that the three vaccines generate a rapid and intense immune response against SARS-CoV-2, neutralizing antibodies had elevated titers in participants at 28 days, who increased and remained stable with a second dose, although each of them have been tested in different numbers and populations, applying recombinant adenoviral vectors and chemically inactivated virions with adjuvant and placebo for which they are totally different but with the same purpose to generate memory antibodies against SARS-CoV-2.

Keywords: SARS-CoV-2; Vaccine; ChAdOx1-S; Sinovac's Coronavac; Gam-COVID-Vac.

Resumen

La tasa de mortalidad estimada por la WHO a nivel mundial por COVID-19 ha sido del 5,7 %, mucho mayor que otras enfermedades infecciosas transmisibles, por lo que es fundamental aplicar una vacuna a la población para disminuir la propagación viral, según la OMS existen 23 proyectos en fase clínica etapa III, como las vacunas: ChadOx1, nCov-19, Gam-COVID-Vac, CoronaVac que muestran resultados prometedores en las investigaciones publicadas por la revista The Lancet Infection Diseases, por lo que consideramos correlacionar las tres vacunas y determinar cuál es más segura, genera una mayor inmunogenicidad y una menor reactogenicidad en los participantes voluntarios, para ello realizamos una revisión bibliográfica y un meta-análisis de artículos científicos de alto impacto, concluyendo que las tres vacunas generan una respuesta inmunitaria rápida e intensa frente al SARS-CoV-2, los anticuerpos neutralizantes tenía títulos elevados en los participantes a los 28 días, que se incrementaban y se mantenían estables con una segunda dosis, aunque cada una de ellas se ha probado en número y poblaciones diferentes, aplicando vectores recombinantes adenovirales y viriones inactivados químicamente con adyuvante y placebo por lo que son totalmente distintas pero con el mismo propósito generar anticuerpos de memoria frente el SARS-CoV-2.

Palabras clave: SARS-CoV-2; Vacuna; ChAdOx1-S; Sinovac's Coronavac; Gam-COVID-Vac.

Introduction

On December 31th 2019, the Wuhan-China health commission reported to the WHO, 44 cases of unknown pneumonia, on January 12th, 2020 after a great investigative deployment, the Chinese national health commission publicly shared the genetic sequence nCov-2019 viral¹, on January 30th 2020, the WHO confirms 6,000 cases and 132 deaths in the old world, for which a public health emergency of international importance was declared and on March 11th a pandemic with 118,000 cases of COVID-19 disease in more than 110 countries^{2,3}.

Currently, on September 28th, 2020 has been reported 32 million infected and 991,224 deaths worldwide by the SARS-CoV-2, so immunization is the best way to reduce the number of sensitive hosts and stop the spread of the infectious microorganism thanks to a vaccine⁴.

Vaccination is an indisputable human right that generates a rapid and intense cellular and humoral immune response, there are currently around 20 vaccines to prevent deadly diseases since it is the best way to protect and control the population, it reduces the spread and source of contagion of the microorganism, that is why we have worked tirelessly to develop a vaccine against SARS-CoV-2⁵.

To date, 250 projects are being developed that try to establish a vaccine that generates a rapid immune response that does not cause adverse effects in patients, 137 vaccines are candidates by the WHO in preclinical development and 23 vaccines are already being tested in clinical trials in humans⁶.

The most relevant vaccines are: ChAdOx1 nCoV19 (AZD1222) manufactured by the University of Oxford / AstraZeneca which is in phase III, the vaccine is based on a Non-Replicating Viral Vector Adenovirus, which by Genetic Engineering and recombinant technology the glycoprotein has been inserted Spike "S" from SARS-CoV-2⁷, forming a hybrid that activates the primary Humoral Immune Response mediated by B Lymphocytes, that immediately generate Antibodies and a Secondary Cellular Immune response mediated by antigen-presenting dendritic cells⁸.

The Sinovac's Coronavac vaccine manufactured by the Chinese biopharmaceutical company Sinovac Biotech Ltd. Which is in phase III, it is based on a complete SARS-CoV-2 virion which is chemically inactivated by -Propiolactone, synthesized in cell culture in Vero cells and purified, to be taken up by dendritic cells or macrophages that triggers a response of TH2 lymphocytes and expression of the immunogen as if it were a natural infection, aluminum hydroxide is used as adjuvant, which increases immunogenicity by stimulating Toll-like receptors, TLRs that activate the inflammasome and antigen-presenting cells^{9,10}.

The Gam-COVID-Vac or Sputnik V vaccine uses a recombinant Non-Replicating Viral Vector Adenovirus (rAd26-S + rAd5-S), 2 types of formulations have been developed, the first is frozen (Gam-COVID-Vac) and the second is lyophilized (Gam-COVID-Vac-Lyo) which were manufactured by the National Research Center for Epidemiology and Microbiology NF Gamaleya (Moscow, Russia)^{11,12}, by genetic manipulation of these vectors, the gene that expresses the glycoprotein "Spike" of SARS-CoV-2 has

been inserted and they lack replication genes, so there is no risk of infection in the organism, this immunogen induces the activation of the cellular response represented by specific cells of the antigen, the cytotoxic T lymphocytes "CD8" and helper T lymphocytes "CD4", which increase the secretion of interferon and activate the humoral response with IgM antibodies^{12,13}.

Three vaccines with promising proposals and with satisfactory results in phase III clinically tested in humans, although each one has important characteristics that make them peculiar and we will detail them in the following bibliographic review.

The main objective of this article is to determine which of the three vaccines generates a greater cellular and humoral immune response in addition to its safety in preventing SARS-CoV-2 infection. The manufacture, host immune response and adverse effects of the three vaccines proposed and considered by the WHO are also described.

Our study will help to understand how immunization activates the host's immune response to generate a rapid and intense defense against SARS-CoV-2.

Methods

This work is a systematic review of high-impact scientific articles, a meta-analysis and data collection of current articles was carried out, the search yielded a total of 80 articles of which 25 were chosen to explain about the projects of vaccination for SARS-CoV-2. Scientific opinion articles were discarded since they have no scientific evidence.

Information sources and search strategy

An exhaustive bibliographic review was carried out in bibliographic search engines such as Scopus, Web of Science, PubMed, Elsevier, ClinicalKey, as well as high impact journal such as The Lancet Infection Diseases, Nature Reserch, Science research Journal, Clinical Trials, searching for keywords like: "SARS-CoV-2" "Vaccine" "ChAdOx1-S" "Sinovac's Coronavac" "Gam-COVID-Vac"; the search began on September 1th, 2020.

The articles were selected according to the title and the abstract, the clinical trials, the phases in the clinical stage, the manufacture of the vaccine, the sides effects they produce and the total number of volunteer patients who received the immunization were included. Furthermore, a qualitative synthesis of the results was carried out and the efficiency and efficacy of the ChadOx1 nCov-19, Gam-COVID-Vac, CoronaVac vaccines were correlated.

SARS-COV-2 and immune response

SARS-CoV-2 is an enveloped positive polarity single-stranded RNA virus, it has glycoproteins on its surface such as the Spike protein (S), which recognizes and binds to the ACE-2 receptor on the cell membrane of type II pneumocytes and vascular endothelial cells⁷, said glycoprotein plays an important role in cell tropism and because it is the target of neutralizing antibodies, drugs and vaccines, in addition its RNA genome encodes 3 structural proteins such as the envelope (E), membrane (M), and nucleocapsid (N)¹⁴.

An RNA virus, with a high rate of spread and genetic variation with mutations that it has acquired in recent months, mainly in its ORF1ab polyprotein, surface glycoproteins, nucleocapsid, as well as deletions in the genome¹⁵, these mutations are produced by a copy error at the time the virion replicates within the host cell¹⁶.

Viral replication triggers a rapid activation of the innate immune response that increases the expression of genes associated with interferon, dendritic cells and macrophages, due to the recognition of molecular markers associated with surface glycoproteins, this immunomodulatory factor is related to the Toll-like receptor (TLR) that activates the adaptive response^{17,18}.

The cellular response represented with cytotoxic T lymphocytes and Natural killer control the progress of the disease by secretes cytotoxic IFN- that activates pro-inflammatory and procoagulation processes, as well as B lymphocytes that generate antibodies such as immunoglobulins and because it is a -CoV virus with several mutations. It is now seasonal there is a possibility that it can cause repeated infections throughout life^{19,20}.

Vector models: ADV, BACULOVIRUS, HERPES VIRUS

Different vaccines have been manufactured using Molecular Biology and Genetic Engineering that produce an active immunization using attenuated mutants or hybrid viral vectors that mimic natural infection and stimulate the Innate and Adaptive Immune Response mediated by antibodies and T lymphocytes in a rapid and massive way, they are safe and stable^{5,21}.

Vectors are previously inactivated by heat or chemical compounds, among the most used are strains of adenovirus, canarypox, vaccinia, poxvirus, in these laboratory prototypes genes that express virulence are inserted and trigger a specific response against the antigen, improves immunogenicity by activating a cellular and humoral response, although it should be mentioned that immunity does not last a lifetime so booster doses would have to be applied²¹.

Adenoviral vectors are the most widely used to carry out vaccines due to the ease of manipulating them and generating mutants, as replace the E1A and E1B genomic region with an expression cassette of a different antigen that replicates in HEK 293 cell cultures and induces a CD8 + T cell response^{5,11}.

Clinical trials of vaccines

VACCINE "ChadOx1 nCov-19 AZD1222"

The University of Oxford together with the pharmaceutical com-

pany AstraZeneca have manufactured a vectorized vaccine with chimpanzee adenovirus that expresses the glycoprotein "S" of SARS-CoV-2. Previously, Oxford University already had studies against the SARS-CoV-1 and MERS coronaviruses, as well as in vitro and in vivo studies with murine and Rhesus macaques⁷.

On August 13, a preliminary report of Phase I / II was published, it was a controlled job, randomized study of simple bias with a total of 1077 participants, 536 women and 541 men who were administered a dose of 5×10^{10} viral particles of the ChadOx1 nCov-19 AZD1222 vaccine and 38% of the patients received a meningococcal conjugate vaccine called Men CWY at a dose of 0.5 mL as a control^{7,8}.

The patients had an age range of 18 to 65 years who have authorized the examinations by giving their consent, without respiratory symptoms that give negative to RT-PCR tests and with negative IgG antibody titers for SARS-CoV-2, infectious and autoimmune diseases, as well as previous respiratory and cardiovascular diseases⁷.

Manufacture of the vaccine "ChadOx1 nCov-19"

To manufacture the vaccine, a recombinant adenovirus vector was used that inserted the SARS-CoV-2 peak protein, previously the codon was purified for expression in human cell lines and a sequence that activates tissue plasminogen (tPA) and encode amino acids 2-1273 of SARS-CoV-2^{7,22}.

Having the sequence synthesized, it was settled in an expression vector, a shuttle plasmid composed of two origins of replication (ORI) was used, in which an early promoter of modified human cytomegalovirus was encoded with tetracycline operator sites (TetO) and polyadenylation signals where the SARS-CoV-2 antigen expression cassette is inserted into the adenovirus E1 locus⁷.

The bacterial artificial chromosome "BAC" was separated from the adenovirus genome to develop into T-Rex 293 HEK cells, and the expression of its pathogenic antigens can be repressed as well as purify the viral titles, to not cause damage within the host cell and activate the host's immune response^{7,23}.

Immunity response "ChadOx1 nCov-19"

To determine how the humoral immune response of the patients developed, the total IgG immunoglobulin was quantified by ELISA before the vaccination process and 28 days later, as well as the cellular response by an enzyme-linked immunospot assay, it is worth mentioning that the vaccines vectored induce a strong cellular response and increase booster antibodies^{7,17}.

The cellular response of the patients represented in specific T cells was activated by recognizing the peak glycoprotein with an exponential titer at 14 days, while the IgG immunoglobulin achieved a receptor binding domain of the peak glycoprotein increasing at 28 days. After that, a booster with a second dose was administered, the concentration of neutralizing antibodies was determined at 42 days^{7,8,17}.

90% of the patients generated neutralizing antibodies at 56 days. Until now, the duration of the immune response that patients can generate is not known²⁰.

Adverse effects "ChAdOx1 nCov-19"

The severity of adverse effects is classified under the following criteria: mild, moderate, severe, life threatening 50% of patients developed muscle pain, local tenderness, fatigue, chills, fever sensation of 38°C that was controlled with paracetamol⁷.

Transverse Myelitis

In September 2020 in clinical phase trials, a supposedly healthy 37-year-old woman developed transverse myelitis after receiving a second dose of ChAdOx1 nCov-19 vaccine, she presented an inflammation of the spinal cord, this neurological disorder progressively degrades the myelin of the cellular nerve fibers causing pain, muscle weakness, paralysis and sensory problems, but upon subsequent examinations the woman suffered from multiple sclerosis^{7,24}.

PHASE III "ChAdOx1 nCov-19"

To enter phase III, the following have been taken into account: the correct surveillance of asymptomatic infection between vaccinated and unvaccinated people, the risks of adverse effects and an increase in the disease, and a comprehensive transparent assessment of the risk that the participants may have²⁵.

Due to the great results obtained in phase I and II, a multicenter randomized double-blind controlled study was designed to apply the ChAdOx1 AZD1222 vaccine to 50,000 participants, a placebo control was used, the study began on August 17th and the first stage is estimated to end on December 2th, 2020 while the project ends on October 5th, 2022, there are some countries that will participate in this study such as Great Britain, the United States, Brazil, South Africa and Japan²⁵.

In experimental phase III, children aged 5 to 12 years and adults aged 18 to 70 years were administered 2 intramuscular doses of 5×10^{10} viral particles or placebo of saline solution to a control group of 10,000 participants at 4 weeks difference, to assess reactogenicity²⁵.

VACCINE "Gam-COVID-Vac or Sputnik V"

The National Research Center of Epidemiology and Microbiology NF Gamaleya (Moscow, Russia), manufactured a vectorized vaccine of Recombinant adenoviruses rAd26 and rAd5 in two studies in phase I and II with a freeze-dried and frozen formulation, which included the participation of 76 participants with an age range of 18-60 years^{11,26}.

The two studies began on June 17th, 2020 and ended on August 10th, 2020 and were carried out in two stages belonging to phase I, which consisted of giving a vaccine (rAd26) to 9 people, to the other 9 the vaccine (rAd5) and in stage 3 place the Prime-Boost vaccination on the 20 remaining participants, which consisted of placing the first component (rAd26) on day zero and the second component (rAd5) on day 21^{11,26}.

Doses of 10^{11} viral particles were administered, of the mutant (100 TCID₅₀) made up of the adenoviral vector combined with Gam-COVID-Vac (rAd26-S) and on day 21 the component (rAd5-S) while the placebo in doses of 0,5m¹¹.

Manufacture of the vaccine "Gam-COVID-Vac"

Recombinant adenoviral vectors (rAd26 and rAd5) were used

to manufacture the vaccine, previously the sequence responsible for its replication was inactivated so that it cannot develop within the host cell and at the same time it stimulates the immune response generating an active immunity by the Spike "S" spike glycoprotein inserted into the E1A genomic region¹¹.

For the formulation of the vaccine, 2 presentations were made, a frozen Gam-COVID-Vac and a lyophilized one that does not require a cold chain for its conservation, although with a higher cost due to the resources and time in its production^{23,26}.

Immune response "Gam-COVID-Vac"

The formation of T helper cells (CD4) and T-killer (CD8 +) was determined, showing a significant increase as well as the levels of interferon gamma in mononuclear cells in 100% of the cases, independently of the adenovirus (rAd26-rAd5)²⁶.

The humoral response represented with neutralizing IgG antibodies was quantified at 14 days with an exponential increase in 88.9% of the patients who were administered rAd26 and 84.2% in the patients who were administered rAd5²⁶.

It is worth mentioning that the neutralizing antibody titers against SARS-CoV-2 were lower than those detected in the ChAdOx1 vaccine from Oxford Astra Zeneca.

PHASE III "Gam-COVID-Vac"

Phase III clinical trials began on September 7th, 2020, the estimated completion date is May 1th, 2021, the study is designed to apply to 40,000 participants from the Russian Federation in which 30,000 participants were given the vaccine and 10,000 the placebo, as well as in Belarus there are 100 participants, the Gam-COVID-Vac vaccine will be administered to 75 participants and 25 participants will receive the placebo²⁷.

The most relevant Inclusion criteria were: people between 18 and 60 years of age with negative antibody titers for infectious tests and a negative PCR test for SARS-CoV-2, who do not have chronic systemic infections, allergies or pregnant women while the criteria of exclusion were patients who have received immunization, vaccines or corticosteroids in the last 30 days²⁷.

ADVERSE EFFECTS "Gam-COVID-Vac"

There were few adverse effects produced by the Gam-COVID-Vac vaccine such as hyperthermia, headache, asthenia, muscle and joint pain that occurred after the second administration of the vaccine that resemble other recombinant vectorized vaccines²⁶.

VACCINE CoronaVac NCT04352608

The vaccine CoronaVac was developed by the Chinese biopharmaceutical company Sinovac Biotech which is based on a complete virion of chemically inactivated SARS-CoV-2 and to increase its immunogenicity an adjuvant composed of aluminum hydroxide, three controlled trials in two phases were carried out that began on 16th of April 2020, the first investigation in phase I had the participation of 144 people with an age range of 18 to 59 years and phase II with 600 participants from China⁹. The second study with phase I / II with 422 participants over 60 years of age and a third study with 552 participants from 3 to 17 years of age that is estimated to end May 30th, 2021¹⁰.

VACCINE MANUFACTURING " CoronaVac "

The CoronaVac vaccine is based on the complete virion SARS-CoV-2 chemically inactivated by γ -Propiolactone and sodium chloride, previously a cell culture with Vero cells was used for its replication and purification of glycoproteins that activate the cellular response and neutralizing antibodies of the host, finally phosphate saline (PBS) was used as buffer^{9,23}.

IMMUNE RESPONSE " CoronaVac "

To determine the immunological safety of the vaccine, the neutralizing antibody titers were quantified on day 28 after the administration of the dose, noting a small increase that increased significantly with the second dose, it is worth noting that the quantified neutralizing antibody titers were related with age the patients^{28,29}.

PHASE III " CoronaVac "

In phase III, 2 studies are being carried out that began on July 31th, 2020 and are expected to end in October 2021, The first was carried out in Brazil with 8870 participants over 18 years of age, and the second study in Indonesia with 1620 participants between 18 and 59 years of age, in both investigations the adjuvant vaccine and a placebo control group were administered⁹.

Participants received 1 dose of 3 μ g / 0.5 ml of the inactivated SARS-CoV-2 vaccine and a second dose at 14 days, while the control group received 2 doses of placebo with an antigen-free diluent at 14 days intramuscularly⁹.

It is emphasized that the study has to be applied to patients with comorbidities, of different ethnicities and older age groups.

ADVERSE EFFECTS CoronaVac "

Pain, swelling, redness, rash, itching resolved within 72 hours of vaccine application, no adverse reactions was observed in grade 3⁹.

Discussion

In the report of October 16th, 2020 the WHO confirms 39,023 292 confirmed cases with SARS-CoV-2 and 1,099 586 death from COVID-19³⁰. As an emerging virus, studies have been carried out to manufacture a vaccine that can reduce the spread and mortality rate worldwide, to date the WHO has considered the work of 23 Institutions that have manufactured a vaccine that is being tested in the clinical phase. In this study, 3 vaccines that are in phase III in clinical studies were considered, published in the journal The Lancet infection diseases and in the first places according to the WHO^{4,6}.

The ChAdOx1 nCoV-19 vaccine is the most accepted vaccine by the scientific community since it is safe, generates high immunogenicity and low reactogenicity if the participants are controlled with paracetamol, in addition, in phase I / II it demonstrated a considerable increase in neutralizing antibodies at 14 days that increased with a second dose, unlike the vaccine Gam-COVID-Vac generates a greater increase in an adaptive immune response mediated by T lymphocytes but with antibody titers lower than the Oxford vaccine^{7,17}.

It should be considered that the ChAdOx1 nCoV-19 vaccine was applied to a total of 1077 participants in phase II and 90% of them developed immunogenicity, while the vaccine Gam-COVID-Vac was only applied to 76 participants of which 100% developed a strong immune response at 28 days even greater than that developed by convalescent patients and the immune response developed by patients who have received the CoronaVac vaccine is related to their age^{7,26}.

In the Oxford clinical studies, 80% of participants developed mild adverse effects after immunization that were easily controlled, while in the study of Gamaleya 50% of the patients developed the same clinical picture since the two vaccines are recombinant adenoviral vectors, as well as the CoronaVac vaccine that has gone through two very controlled phases with a total of 1718 participants who have had very little pain, redness in the inoculation area that has been resolved within 72 hours^{7,9,26}.

It has been considered a hypothesis to apply a single dose with a higher concentration of viral particles, although this does not ensure that immunological memory antibodies are generated, there are many questions about vaccines but the fact that they are in phase three and in such a short time it is an achievement for the scientific community and the world population^{7,9}.

The cellular and humoral immune response generated by the three phase I / II vaccines has been strong and tolerated by 90% of the participants, there is no reactogenicity if the symptoms are controlled with paracetamol, the adverse effects have been mild and phase III is expected to be completed with favorable results for the thousands of participants from different countries^{17,29}.

Conclusions

1. The ChadOx1 nCov-19 vaccine from Oxford / Astra-Zeneca is the one that has had the best results because it has had a largest number of participants, 2 doses have been administered with a strong cellular and humoral response with neutralizing antibodies that has remained constant for 56 days.
2. The vectorized recombinant adenoviruses vaccine Gam-COVID-Vac, from Gamaleya (Moscow / Russia), has had only 76 participants in phase I / II, it has generated a significant increase in the levels of T lymphocytes (CD4 and CD8) greater than the VaccineChadOx1 nCov-19, although the humoral response progressively increased but only in 88.9% of the participants.
3. The CoronaVac vaccine of an inactivated SARS-CoV-2 whole virion, from Sinovac Biotech, China was administered to 1166 participants with favorable results at 28 days, the neutralizing antibody titers were stable as well as the cellular response although they were inversely correlated proportionally with the age of the patients.
4. The vaccination process is the best way to control the spread of SARS-CoV-2 and reduce infection in asymp-

tomatic hosts, there are many biopharmaceutical companies that have created a vaccine but phase III results are needed to verify which one generates a vaccine with the highest immunogenicity with low reactogenicity.

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