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The Safety and Effectiveness of mRNA-1273, BNT162b2, BNT162b1,ChAdOx1-nCoV-19 Vaccines Against Covid-19

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Abstract

COVID-19 disease is an infectious disease caused by the SARS-CoV-2 virus which has become a pandemic in the last year and a half. Because of this virus since October 2019, more than 1,000,000 deaths have been caused and for this it was imperative to develop a drug or vaccine. SARS-CoV-2 usually causes mild to moderate symptoms in most people such as dry cough, fever, myalgias which are similar to the symptoms of the flu virus. Also, many people who are infected with the virus do not show any symptoms, they are carriers of it and this is the main cause of its global spread. Vulnerable groups consisting of the elderly, people with chronic or underlying diseases, pregnant women and young children are at the highest risk due to their weakened immune system and often need hospital treatment in case of COVID-19 disease. The main purpose of this literature review is to evaluate the safety and efficacy of some vaccines developed against COVID-19, namely the Pfizer (BNT162b1 and BNT162b2), Moderna (mRNA-1273) and AstraZeneca (ChoOX1) vaccines. -19). The materials used in the articles were each experimental vaccine separately in different doses (or not), the placebo vaccine selected in each study and some methods of measuring the immune response such as measuring IgG or measuring cellular responses or measuring of the interferon-c intermediate. The results of the six articles analyzed showed that all vaccines were considered sufficiently safe for use as they showed mainly local reactions lasting a maximum of 48 hours and systemic reactions were minimal. In fact, the side effects in all 3 vaccines were milder in the elderly group than in younger people. Regarding the efficacy after the administration of both doses, it seemed that the highest is available from the Pfizer vaccine (95%), then Moderna (94.1%) and finally AstraZeneca (63%). Note that the immune response elicited by all 3 vaccines was almost the same for all age groups. However, the selected articles also had some limitations such as that they did not include all or none of the vulnerable groups or that the participants were not from many different countries or that the number of people was not large enough to be generalized with certainty all the conclusions. Therefore, further studies that follow will review these results by removing all existing limitations. In conclusion, the data obtained on vaccines appeared to be quite encouraging in tackling the pandemic through prevention and especially in protecting vulnerable groups that are a priority.

Introduction

COVID-19 disease is an infectious disease caused by a newly discovered coronavirus. People who are infected with the new virus are more likely to develop a mild to moderate respiratory illness and recover without specific treatment. However, people with chronic medical problems (cardiovascular disease, diabetes, etc.) as well as the elderly are more likely to develop the disease more seriously, need to be admitted to the Intensive Care Unit (ICU) and may even commit death (Esakandari et al., 2020). It is now known that COVID-19 is spread mainly through saliva droplets or nasal secretions when an infectious person sneezes or coughs (Singhal, 2020). Since vaccinations have started, but

most of the population is still unvaccinated and the cure for the virus has not yet been discovered, each of us must be protected by following the exact guidelines of the World Health Organization (WHO) according to which the systematic hand washing, avoiding contact of our hands with any part of the face especially when we have touched an object and using the elbow in case of coughing or sneezing. In general, keeping distances greater than two meters and the use of a mask and gloves both indoors and outdoors is mandatory. This study will look at the safety and effectiveness of the recent discovery of the vaccine for both mRNA and DNA, which is the only "weapon" for killing the virus. The term safety refers to a situation in which the potential hazards to humans have been reduced to an acceptable level. Efficacy is the maximum achievable biological response that the vaccine can elicit.

Coronaviruses are a large family of viruses known to cause diseases ranging from the common cold to the most serious diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). We now know that there are seven different types of coronavirus (Yin and Wunderink, 2017) among the most important is SARS-CoV-1 which appeared in southern China in late February 2002 and according to scientific research seems to have been transmitted from cats to humans (Shi and Hu, 2007). The coronavirus, like this year and in 2002, spread to many countries before being brought under control. Also, the Middle East MERS-CoV syndrome that first appeared in mid-2012 which is a viral respiratory infection (Chafekar and Fielding, 2018) as well as the prevailing SARS-CoV-2 in our time has caused one of the biggest pandemics of all ages. It has also been found that several young coronaviruses are circulating in animals and have not yet infected humans.

Severe Acute Respiratory Syndrome (SARS) is a viral respiratory disease of zoonotic origin that appeared in the early 2000s and was caused by severe acute respiratory coronavirus syndrome (SARS-CoV-1). In 2003 a SARS epidemic started in China and spread to other countries before it ended in 2004. The virus that causes COVID-19 is similar to the one that caused SARS in 2003 and both are coronavirus types. COVID-19 has spread faster than SARS-CoV-1. It took 13 full years for Chinese scientists in late 2017 to detect the virus, which originated from horseshoe bats that live in a cave in Wuhan Province. It is a fact that no cases of the first SARS-CoV worldwide have been reported since the 2004 epidemic. In 2019, its successor was discovered, the associated strain of the severe acute respiratory syndrome virus now called SARS-COV-2. This new strain causes COVID-19, a disease that caused the 2020 pandemic. The symptoms of SARS-CoV-1 are similar to SARS-CoV-2 and mostly look like the flu, including fever and muscle aches, lethargy, cough, sore throat and other non-specific symptoms (Pascarella et al., 2020). The only symptom common to all patients appears to be fever over 38 º C. SARS can lead to shortness of breath and pneumonia, either direct viral pneumonia or secondary bacterial pneumonia. It is known that the average incubation period for SARS is 4-6 days although it can rarely be very short from 1 day or up to 14 days (Lauer et al., 2020). Note that the mortality rate of SARS-CoV-2 is 3.4% and is more common in men than women.

The SARS-CoV-1 vaccine was not discovered although some clinical trials had begun in 2004 and were discontinued due to lack of funding. The SARS-CoV-2 vaccine was discovered in late 2020 thanks to advanced technology and applying all clinical stages to be considered safe and effective. In fact, there are mRNA and DNA vaccines which in this article will be evaluated for their safety and effectiveness through clinical trials.

MRNA vaccines contain mRNA fragments that are responsible for producing harmless, virus-like proteins from our cells. This is done after the mRNA enters the ribosomes and the translation process is carried out to express the S-pin glycoprotein and trigger the production of neutralizing antibodies and cellular immune responses, which contribute to the protection against Sars-Cov-2 that induces COV-19. The cells destroy the genetic material of the vaccine within a few days and if exposed to the virus the antibodies will attach to the Sars-Cov-2 protein spikes and remove its ability to infect them. Specifically, one of the discovered mRNA vaccines for SARS-CoV-2 is that of Pfizer (Code BNT162b2) which commands the synthesis of the virus spike protein which causes strong antigenic stimulation. Thus, when these proteins are produced, the immune system recognizes them as "foreign" and produces specific T and B lymphocytes that have immune memory and can destroy the virus if it enters the body. Of course, mRNA does not enter the body directly on its own because due to its high

hydrophilicity and negative charge it can not cross the cell barrier and so thanks to the advanced technology of the time it managed to complex with cationic lipids and ensure its stability (Brito et al., 2014). This vaccine is administered intramuscularly in two doses with an interval of 3 weeks and its storage conditions are at -70ºC for up to 6 months. Some side effects that have been reported are pain, swelling in the arm area where the vaccine was given, fever, chills, nausea and headache. Contraindications to this vaccine are allergy to polyethylene glycol (PEG) or polyisosorbide which are components of the mRNA vaccine and if an allergic reaction occurs after the first dose. Also, the duration of the immunity it offers has not been clarified yet as it should be some time after the vaccination of humans and additional studies should be done in this regard. Finally, its effectiveness is estimated at 95% (Meo et al., 2021). The Moderna vaccine has a similar effect as it does mRNA.

The Astra Zeneca vaccine (Code AZD1222) is the DNA vaccine discovered against COVID-19 which is administered intramuscularly in 2 doses over 4 weeks. It can be stored at -20ºC for 6 months and vaccinated in people over 18 years. Until a few months ago, people over the age of 65 were contraindicated, but now, according to new WHO data, people between the ages of 65 and 75 have started to be vaccinated in many countries. The genes encoding the virus spike protein have been integrated into another adenovirus. The adenovirus used is Ch.Ad.Ox1 which can enter cells but not multiply in them. After intramuscular injection into the arm the adenovirus enters the cells and is promoted to the nucleus so that it integrates with the cell DNA. Thus, the gene responsible for the spike protein begins to be transcribed into the corresponding mRNA which is transferred to the cytoplasm and then translated and the protein is produced. It is expressed on the cell surface and is recognized by dendritic cells which are antigen-presenting and will present it to the T-helpers that stimulate B-cells to produce antibodies. The antibodies produced are capable of blocking the entry of the spike protein into other cells and at the same time activate the natural killer cells that destroy any cell that has been infected with a coronavirus. Surprisingly, one dose of this vaccine has been found to be 90% effective while both are 62% effective.

The reason why this topic was chosen is that it concerns the current world and concerns every day, apart from researchers, all conscientious citizens who seek answers to their many unanswered questions.

The research question of this work which will be answered below is: How safe and effective are the vaccines against COVID-19 and specifically of Pfizer, Moderna and AstraZeneca? The main purpose is the literature review of clinical trials in healthy individuals of different age groups to evaluate the safety and efficacy of Pfizer, Moderna and AstraZeneca vaccines in the human body for the prevention of COVID-19. At the same time, the individual goals are:

- the evaluation of the safety and efficacy of ChAdOx1 nCoV-19, BNT162b2 and mRNA-1273 in individuals from different countries aged 18-55 years and in clinical phases 1/2, 2/3, 3.
- the safety and efficacy of vaccines in people over 70 years of age
- the protection they provide to people with underlying diseases
- the protection they provide to people living in high-risk areas
- the effectiveness of the above vaccines in different doses
- their evaluation based on the results of other placebo drugs
- the comparison between them

Research Methodologies

Research methodology is generally a process in which observable, confirmed and systematically collected data from the world are used in order to describe, interpret, predict or even control a phenomenon. The research is divided into quantitative and qualitative, where the first is a formal, systematic and objective process that uses numerical data in order to describe, interpret, predict and control various phenomena. It is also done with meticulousness, objectivity and is governed by rules in order to ensure the representativeness of the sample and to reduce the influence of exogenous factors. The researcher does not participate or intervene in the process but formulates specific goals and tests specific hypotheses based on existing scientific knowledge. Regarding the second category of research, it is a subjective approach that does not use numerical data and deals with complex

psycho-social phenomena. Therefore, the researcher has an active role in this process as the results are influenced by his views (Noula 2021).

Generally for Covid-19

The COVID-19 pandemic is a topical issue that concerns scientists and the world as it has caused a huge problem in the health system, hundreds of thousands of people have lost their lives and there is a global financial blow. The only way to prevent the virus at the moment is to vaccinate all the people where it is started but it is necessary to study the safety and effectiveness of both the DNA and the mRNA vaccine.

Study of Voysey Et al.,

Voysey et al., (2020) examined the safety and efficacy of the Astra Zeneca DNA vaccine in individuals over 18 years of age through four ongoing, blind, randomized, controlled clinical trials. The study took place in the United Kingdom, Brazil and South Africa. In this experimental study, participants were randomly divided into the ChAdOx1 nCoV-19 experimental group administered the vaccine and the control group administered saline. From April 23 to November 4, 2020, 23,848 participants were included in the study, of which 11,636 were included in the primary vaccine efficacy analysis. Participants in the ChAdOx1 nCoV-19 group received 2 doses containing 5x1010 viral particles (standard dose) and a subset of individuals in this trial in the UK received half dose as first dose (low dose) and one standard dose as second dose. Substantial efficacy analysis showed that seronegative participants after 14 days of the second dose of the vaccine were found to be symptomatic of COVID-19 following a DNA analysis test. Participants were analyzed based on the treatment they received for their symptoms and the effectiveness of the vaccine was calculated as a relative risk arising from a model called Poisson that is age-appropriate. This means that there was no difference in the risk between the control group and the experimental group. Participants receiving two standard doses reported an efficacy of 62.1%, while participants receiving a low dose and a standard dose received 95%. The overall efficacy of the vaccine in both groups was 70.4%. At the same time, it was observed that there were 10 people from the control group where 3 weeks after the first dose they were treated with COVID-19 including one death. During 3-4 months of vaccine safety monitoring, 175 adverse reactions were recorded in 168 subjects, of which 91 were from the control group and 84 from the experimental group. Only three events were evaluated as possibly vaccine-related, one in the control group, the other in the ChAdOx1 nCoV-19 group, and the latter has not yet been recorded in which group it belongs. In conclusion, ChAdOx1 nCoV-19 has been shown to have an acceptable safety profile and has been found to be effective against symptomatic COVID-19 in this interim analysis of ongoing clinical trials.

Study of Ramasamy Et al.,

Another study by Ramasamy et al., (2020) conducted at two UK research institutes investigated the safety and efficacy of the ChAdOx1 nCoV-19 vaccine in adults over 18 years of age and older adults over 70 years of age. A single blind, randomized, controlled phase 2/3 was performed. Between May 30 and August 8, 2020, 560 participants registered. Individuals were selected if they did not have severe comorbidities (diabetes, history of allergic reactions) or high weakness (aged 65 and over). They were divided into 3 subgroups according to their age where the first group included people aged 18-55 years (160 people), the second people 56-69 years (160 people) and the third age 70 years and over (240 people). Participants were given a low dose and then randomly selected for each age group as to whether they would receive ChAdOx1 nCoV-19 intramuscularly at a dose containing 2.2x1010 viral load or whether they would receive the controlled MenACWY vaccine. The MenACWY vaccine is approved against meningococcal groups A, C, W, Y and has been given regularly to adolescents in the UK since 2015 as it protects against one of the most common causes of meningitis and sepsis. This vaccine is also given to travelers to high-risk countries. This vaccine was used as an “active control vaccine” in this study to better understand the response of ChAdOx1 nCoV-19 participants. The reason a saline was not used is because some minor side effects are expected from the ChAdOx1 nCOV-19 vaccine such as sore throat, headache and fever. Saline does not cause any of these side effects. If participants received only this vaccine or saline and continued to develop side effects, they would know they had received the new vaccine. It is crucial for this study that participants do not know whether or not they have received the vaccine because, if they did, it could affect their behavior in community issues after vaccination and may lead to “bias” on its

results study. The procedure included specific ratios for each age group which were: in the 18-55 age group 1: 1 to two doses of ChAdOx1 nCoV-19 or two doses of MenACWY, in the 56-69 age group 3: 1: 3: 1 to one dose ChAdOx1 nCoV-19, one dose of MenACWY, two doses of ChAdOx1 nCoV-19 or two doses of MenACWY and finally in the age group 70 and over the ratio was 5: 1: 5: 1 to one dose of ChAdOx1 nCoV-19, one dose of MenACWY, two doses of ChAdOx1 nCoV- 19 or two doses of MenACWY. From the first group 100 people received the experimental vaccine and 60 people received the controlled one, from the second group 120 people received the experimental vaccine and 40 people received the controlled vaccine and from the third group 200 participants received ChAdOx1 nCoV-19 and 40 participants received MenACWY . Primary aid schemes were given 28 days apart. Participants then received a standard dose of the $3.5\text{-}6.5x10^{10}$ viral load vaccine and the same randomization procedure was repeated except for the 18-55 year old group where it was defined in a 5: 1 ratio in two doses of ChAdOx1 nCoV-19 or two doses. MenACY. The specific objectives of the present clinical study were to evaluate the safety and humoral and cellular immunity of a one- and two-dose program in adults over 55 years of age. Cellular response was measured by performing an ex-in vivo immunoblot assay linked to the IFN-γ intermediate transmitter. The recording of this data showed efficiency but also safety after counting the side effects. Of course, early clinical findings on the safety and cellular response of the vaccine were reported in this clinical study. The results of the study showed that 7 participants did not receive the boost dose of the two-dose regimen assigned to them either because they withdrew from the study or because they were not contacted after the first dose, one participant received the wrong vaccine either the experimental or the controlled and 3 participants were excluded from the study due to an error in the identity of the samples possibly due to an error made in the laboratory during the recording of their data and their samples were confused. Also, 50% of the people with the ability to analyze were women and the remaining 50% were men. It was noted that local and systemic reactions were more common in those who received the experimental vaccine than in those who received the controlled one, but in both cases the side effects were headache, fever, muscle aches and pain at the injection site. In fact, these reactions were less common in people over the age of 56 than in young people. Those who received two standard doses of ChAdOx1 nCoV-19 after the first vaccination reported local reactions in 43 of the 49 participants (88%) in the 18-55 age group, 22 of the 30 (73%) in the 56-69 age group, and 30 out of 49 (61%) in the group 70 years and older. Systemic reactions were present in 86% of the first group, 77% of the second group and 65% of the third group. As of October 26, 2020, 13 adverse reactions have been reported, none of which have been linked to the vaccine. Regarding the immune response, it appeared that those who had been given two doses of the experimental vaccine had a mean IgG secretion of SARS-CoV-2 spike protein that was the same in all age groups 28 days after the boost dose. At the same time, 99% of the participants 14 days after the boost dose were observed to have started T-cell responses which peaked on the 14th day after a standard dose of the experimental vaccine. In conclusion, ChAdOx1 nCoV-19 appears to have better tolerance in older adults than in younger ones and has a similar immune response in all age groups after a boost dose.

Study of Folegatti Et al.,

Another clinical study conducted in 5 different locations in the United Kingdom by Pedro M Folegatti et al., (2020) evaluated the safety, efficacy and immunogenicity of the vaccine through a blind, randomized, controlled, phase ½ test. Specifically, between April 23 and May 21, 2020, 1,077 participants enrolled and received either a single dose of ChAdOx1 nCoV-19 containing adenovirus as a vector (n = 543) or MenACWY (meningococcal) (n = 534) as a controlled vaccine. Healthy adults aged 18-55 years without a history of laboratory-confirmed SARS-CoV-2 infection or COVID-19 symptoms received randomly (1: 1) chAdOx1 nCoV-19 at a dose of 5 × 1010 viral particles or MenACWY as an intramuscular injection. A protocol modification at two of the five sites allowed paracetamol prophylaxis to be given prior to vaccination. Also 10 of the participants underwent a non-randomized group and received two doses of ChAdOx1 nCoV-19 with a difference of 28 days between them. Initiation and post-vaccination responses were assessed by measuring IgG antibodies against the SARS-CoV-2 protein spike. The results were compared with some known COVID-19 cases and safety was measured by the occurrence of serious adverse reactions 28 days

after vaccination. The analyzes were performed by group distribution of participants who received the vaccine. The results of the study were as follows: Local and systemic reactions were more common in the group receiving the experimental vaccine, and many were reduced with the use of paracetamol prophylaxis, such as muscle pain, headaches, fever, and chills. However, there were no serious side effects. In this group, spike-specific T cell responses peaked on day 14 and IgG responses increased on day 28 and were enhanced after the second dose. Neutralizing antibodies to SARS-CoV-2 were detected in 32 (91%) of 35 participants after the first dose when measured by the MNA80 microharmonization assay and in 35 (100%) of 35 participants when measured by the neutralization assay. plate by 50% in PRNT50 (method of measuring the ability of the virus to neutralize the antibodies produced in the body). After the second dose, all participants had neutralizing activity (9 out of 9 on day 42 by MNA80 count). In conclusion, ChAdOx1 nCoV-19 showed an acceptable safety profile and homologous amplification of elevated antibodies. These results, together with the induction of cellular immune responses, support a large-scale evaluation of this candidate vaccine in an ongoing phase 3 program.

In addition to the AstraZeneca vaccine, studies have been performed on both the Pfizer vaccine (BNT162b2) and the Moderna vaccine (mRNA-1273), which are lipid nanoparticle mRNA vaccines that are nucleoside-modulated to encode the the pin (glycoprotein) trimer of SARS-CoV-2.

Study of Polack Et al.,

A study by Polack F et al. (2020) evaluated the safety and efficacy of this vaccine through an ongoing multinational, placebo-controlled, blind study. Specifically, there were 43,548 participants aged 16 years and over who in a ratio of 1: 1 received either the experimental vaccine (30μg per dose) or the placebo vaccine in 2 doses with a difference of 21 days. A total of 43,448 people received injections, of which 21,720 were vaccinated with the real vaccine and 21,728 with the placebo vaccine. There were 8 cases that were infected with COVID-19, 7 days after the second dose while receiving BNT162b2 and 162 cases that were infected but received placebo. There were also 10 cases of severe COVID-19 after the first dose, 9 of whom had taken placebo and 1 had received the actual vaccine. BNT162b2 has been shown to be 95% effective in preventing Covid-19 (95% reliable interval, 90.3 to 97.6). Similar efficacy of the vaccine (generally 90 to 100%) was observed in all subgroups defined in terms of age, sex, race, ethnicity and body mass index. Side effects observed were short-term mild to moderate pain at the injection site, fatigue and headache. The incidence of serious adverse reactions was low and similar to the groups receiving the placebo vaccine. In conclusion, BNT162b2 in two doses offers 95% protection against COVID-19 in people over 16 years of age and the average safety was judged to be similar to that of other viral vaccines.

Study of Walsh Et al.,

Another ongoing randomized, placebo-controlled, phase 1 observer-blind Phase 1 test performed by Walsh et al., (2020) tested the safety and immunogenicity of the BNT162b1 vaccine (encodes a three-dimensional SARS-CoV-2 receptor binding region), and BNT162b2 (encodes a full-length SARS-CoV-2 spike membrane). The study was conducted in the United States and Germany and involved 332 healthy adults aged 18-55 and 65-85, excluding those with an autoimmune disease or HIV, HCV, HBV, COVID-19 or who had already been vaccinated against corona virus or used some kind of medicine to prevent it. Also, participants had to have a negative PCR which they had done within 24 hours before the study. The volunteers were randomly divided through a technological interactive system found on the internet into 13 groups of 15 people each as 195 ultimately met the criteria for inclusion in the study. The distinction was made based on age range, dose amount and vaccine candidates. From each group 12 of the 15 received the real vaccine and the other 3 the placebo. Groups of participants aged 18-55 years and 65-85 years received dose levels of 10μg, 20μg or 30μg BNT162b1 or BNT162b2 in a 2-dose regimen, with a difference of 21 days. A group of participants aged 18-55 years received 1 dose of 100 μg BNT162b1 or placebo. Overall, participants were predominantly white (67% -100%) and non-Hispanic / non-Latino (92% -100%). More older women than older men participated. The median age of the youngest participants was 35-37 years and that of the older participants was 68-69 years. From the results recorded for the safety of the vaccine in terms of local reactions, it was observed that participants aged 18-55 years who received 10 or 30 μg BNT162b1

reported mild to moderate local reactions, mainly pain at the injection site, within 7 days after injection, which was more frequent after the second dose. Between the ages of 65 and 85, BNT162b1 elicited similar but milder local reactions, with mild to moderate pain at the injection site reported 92% after Dose 1 and 75% after Dose 2. Similar results were observed after BNT162b2 vaccination. No elderly adult receiving BNT162b2 reported redness or swelling, and no participants receiving the BNT162 vaccine reported a local grade 4 reaction. Regarding systemic reactions, participants aged 18-55 years who received to moderate fever and chills, with 75% having a fever> 38.0 ° C after dose 2 of 30 µg. In participants aged 65-85 years receiving BNT162b1, systemic events were milder than in younger participants, although many reported fatigue and headache after Dose 1 or Dose 2, and 33% of older participants reported fever> 38 ° C after Dose 2, including an elderly person who reported a fever of 38.9-40.0 ° C. Like local reactions, systemic events were dose-dependent, and greater after Dose 2 than in Dose 1 and transiently. Symptoms generally peaked on day 2 after vaccination and resolved by day 7. Systemic events from BNT162b2 were milder than those of BNT162b1. For example, only 17% of 18-55 year olds and 8% of the 65-85 year old group reported fever (> 38, 0-38, 9 ° C) after Dose 2 of 30 µg BNT162b2. Serious systemic events (fatigue, headache, chills, muscle aches, and joint pain) were reported in a small number of younger BNT162b2 recipients, but were not reported by older recipients. There were no reports of Grade 4 systemic events from any BNT162b2 recipient. Overall, the systemic reactions reported by people aged 65-85 years receiving BNT162b2 were similar to those reported by those receiving placebo after Dose 1. Adverse reactions (ADs) and shifts in the above laboratory values up to 1 month after dose 2, was that 50% of participants aged 18-55 years receiving 30 µg BNT162b1 reported relevant AEs compared to 11.1% of placebo recipients. Between 65-85 years receiving 30 µg BNT162b1 and 18-55 years receiving 30 µg B162b2, 16.7% reported associated AEs. No 65-85 year olds receiving 30 µg BNT162b2 reported an associated AE. The largest changes observed from baseline to laboratory values were transient reductions in lymphocyte counts, which subsided within one week after vaccination and were not associated with clinical manifestations. The results of the immunogenicity of the vaccine were recorded by measuring the IgG values of the participants and compared with the values of 38 people who had SARS-COV-2 and the antibody test was performed at least 14 days after their diagnosis by PCR test. Their ages ranged from 18-83 years. The immune responses elicited by BNT162b1 and BNT162b2 were similar and compared to those seen in individuals with a natural infection were quite encouraging. Neutralizing responses to vaccination with 10 µg to 30 µg BNT162b1 or BNT162b2 were enhanced by Dose 2 in both younger and older adults, with a clear benefit of a second dose. Both vaccines elicited lower antigen-binding IgG response and neutralizing responses in the 65-85 age group compared with the 18-55 age group. Although there was the same response in any vaccine candidate at doses between 10 µg and 20 µg, the response between 20 µg and 30 µg was not the same for all age groups. People aged 18-55 had a higher response than people aged 65-85. Based on the evaluation of the above results, it was decided that the vaccine suitable for promotion was BNT162b2 at a dose of 30 µg between phase 2 and 3 through a global safety and efficacy evaluation in participants aged 18-85 years. This decision was made because there were milder systemic reactions to this vaccine mainly at older ages in the context of comparable antibody values derived from both vaccines.

Study of Baden Et al.,

Another phase 3 study of the Moderna vaccine (mRNA-1273) was conducted by Baden et al., (2021) at 99 centers in the United States. It was a randomized, controlled, blinded study involving 30,420 volunteers aged 18 years and older with no known history of COVID-19 infection in areas at high risk or suffering from underlying diseases, or both. Participants were randomly divided into a 1: 1 ratio (15,210 in each group), using a central system of interactive response technology, to receive a vaccine or placebo. The distinction was made based on the age risk criteria and the complications that COVID-19 disease would cause in the following risk groups: people 65 years of age and older, people under 65 years of age who were at increased risk for severe COVID- 19 and people under the age of 65 without increased risk. Participants under the age of 65 were assessed to be at risk for severe Covid-19 if they had at least one of the following risk factors, based on the Centers for Disease Control and Prevention (CDC) criteria available at the time of test design: a) chronic lung

disease (e.g. emphysema, chronic bronchitis, idiopathic pulmonary fibrosis, cystic fibrosis or moderate to severe asthma) b) heart disease (e.g. heart failure, congenital coronary heart disease, cardiomyopathy or pulmonary hypertension) c) severe obesity d) diabetes (type 1, type 2 or pregnancy) e) liver disease g) human immunodeficiency virus infection HIV. The dose administered was either 100μg mRNA-1273 in 2 doses with a difference of 28 days or placebo «saline». More than 96% received the second dose. Common reasons for the 2.2% who did not take the second dose were withdrawal of consent (153 participants) and detection of SARS-CoV-2 by PCR before the second dose on day 29 (114 participants: 69 in the group). of placebo and 45 in the vaccine group). The results of this study recorded the safety and efficacy of the vaccine. Regarding the first, it was observed that side effects at the injection site were more frequent in the mRNA-1273 group than in the placebo group after the first dose (84.2% vs. 19.8%) and the second dose (88.6% vs. 18.8%). In the real vaccine group, these side effects were grade 1 or 2 and averaged 2.6 and 3.2 days after the first and second doses, respectively. The most common symptom was pain at the injection site. Delayed injection site reactions after the first or second dose were very rare. Systemic adverse reactions were more common in the mRNA-1273 group than in the placebo group after the first dose (54.9% vs. 42.2%) and the second dose (79.4% vs. 36). 5%). Their severity increased after the second dose in the mRNA-1273 group, with increasing proportions of grade 2 events (from 16.5% after the first dose to 38.1% after the second dose) and grade 3 (from 2.9 % to 15, 8%). The required systemic adverse reactions in the mRNA-1273 group lasted an average of 2.9 days and 3.1 days after the first and second doses, respectively. Both injection site and systemic side effects were more common in younger participants (ages 18 to under 65) compared with older participants (over 65 years). The frequency of adverse reactions between the two groups during the 28 days was similar. Also, 3 deaths were recorded in the placebo group and 2 deaths in the real vaccine group. Adverse reactions considered by the test group to be related to the vaccine or placebo were reported between 4.5% of the placebo group participants and 8.2% of the mRNA-1273 group. The most common treatment-related adverse reactions in the placebo group and in the mRNA-1273 group were fatigue and headache. In the general population, the incidence of serious treatment-related adverse reactions was higher in the mRNA-1273 group. The relative incidence of these adverse reactions according to the vaccine group was not affected by age. In terms of its effectiveness, the primary analysis showed that there were a total of 196 cases of COVID-19, of which 185 belonged to the placebo group and 11 to the real vaccine group. Thus, efficacy was estimated at 94.1% for the prevention of SARS-COV-2 infection compared with placebo. The findings of the secondary analysis were similar to the first one including the evaluation performed 14 days after the 1st dose which showed that the effectiveness was 95.2% (225 cases in the placebo group and 11 in the mRNA-1273 group) involving participants who had evidence of SARS-COV-2 infection at the start of the study. Severe cases of COVID-19 occurred in 30 people with one death and all belonged to the placebo group. In conclusion, this vaccine provides protection against SARS-COV-2 with very high efficacy, 94.1% which raises many expectations. However, because the duration of the immunity it creates has not been studied at present, it is considered to be short-term. Regarding the issue of side effects, they are not a serious problem because mainly local reactions at the injection site are reported, which are transient.

Moral Issues

In a research it is necessary to observe all the moral prerequisites as human subjects are used which must be protected by science. In the past, the exploitation of the human species for scientific studies was common, but in 1947 the Nuremberg Code of Ethics was developed by the American Medical Association to stop Nazi doctors' experiments on prisoners' concentration camps. The second internationally recognized code of ethics was the Helsinki Declaration of 1964 to be a guide for research physicians. It was divided into two categories, Therapeutic which the participants will benefit with a therapeutic result and Non-Therapeutic which concerns the development of scientific knowledge without having therapeutic value for the subjects. Then, in order to ensure the ethical principles in any research, they were set in 1978 by the Belmont Report of the National Commission in order to protect people from Biomedical Research in the USA. Thus, the principles that were established were:

- the principle of benefit and non-harm,
- the principle of respect for human dignity,
- the principle of justice.

At the same time, in all cases the basic rights of the research subjects must be protected, which are the following:

- The right not to suffer any kind of harm (physical, mental, spiritual, etc.),
- Right to be fully aware of the process (duration, methods to be used, etc.) and its purpose,
- Right to self-determination, i.e. without pressure, individuals can freely decide whether they want to participate in the study and whether at any time they want to terminate their participation,
- Right to privacy, confidentiality and anonymity.

To ensure all of the above, to inform the volunteers correctly and to avoid misunderstandings, there is a form of "informed" consent which can be filled in by the audited participant if he / she has received the necessary knowledge that will push him / her to participate in the research voluntarily, which is signed by him, the researcher and the research representative.

Therefore, an ethical research that protects human rights must be characterized by scientific objectivity. That is, the scientist should not hide or falsify results which may not be encouraging or even approve of them. He must also fully present the research design to his associates and participants and not deceive them but determine their credibility (Noula, 2021).

In all the articles used for the bibliographic review it is shown and recorded that the above ethical principles were observed and no rights of the subjects were violated.

Conclusions and Discussion

The study by Voysey et al. (2020) found that the ChAdOx1 nCoV-19 vaccine evaluated in four trials on three continents was 70.4% effective after two doses and 64.1% after at least one standard dose. without much concern for his safety. In fact, it was observed that in participants from both the United Kingdom and Brazil the efficacy was 60.3% and 64.2% respectively and it is worth noting that the second dose in the United Kingdom was taken 12 weeks after the first and in Brazil after 6 weeks. It appears that the time difference between doses had no significant effect on efficacy. In addition, a similar response was recorded in individuals over 70 years of age with those aged 18-55 years. Other published results for COVID-19 vaccines, namely Pfizer BNT162b2 mRNA (Pfizer INC, 2020; Palagin, 2021) and Moderna mRNA-1273 showed 92% and 94.5% efficacy respectively. However, one study found that if a vaccine is 60-80% effective it can have a significant impact on public health (Bartsch, 2020) and ChAdOx1 nCoV-19 exceeds that percentage. It is also quite encouraging to approve more than one vaccine against COVID-19. Regarding the side effects of this vaccine, some local and systemic reactions were reported, but they were tolerated in older adults even after the second dose. However, there were three serious cases of adverse events (2 in the real vaccine group and the other in the placebo group) and in particular transverse myelitis which after examination revealed that only one in the experimental group could be related to the vaccine, which will be studied in future research.

The results of a study by Ramasamy et al., (2020) showed that ChAdOx1 nCoV-19 has a safe profile that causes fewer reactions in the elderly than in the younger. Immunogenicity was similar in all age groups which is very encouraging as older people are at the highest risk for SARS-COV-2 and if a vaccine is approved it should not be effective in them. Most of the local and systemic adverse reactions observed were milder than in the Phase I study for the same vaccine (Folegatti, 2020) included in this literature review. Serious adverse reactions observed in this trial were considered unrelated to the vaccine and occurred at normal frequencies as expected in a general population. In terms of immunogenicity, compared to other studies involving older groups, it appeared that there was a reduced number of antibodies compared to younger age groups (Zhu, 2020). However, this study did not include 2 doses like the others, but only one. Therefore, a complete comparison cannot be made on this piece. However, the results can be compared with other studies of adenovirus vaccines as a carrier against the RSV virus that infects the human respiratory system and showed that administering a single dose showed very high antibody values in elderly participants (Williams, 2020). At the same time, comparing the results of a study by Ramasamy et al., (2020) with a vaccine containing the same

ChAdOx1 influenza vector, a similarly high immune response is observed in the elderly (Coughlan, 2018).

Through the literature review it was observed that ChAdOx1 nCoV-19 when administered in a single dose in the clinical study of Folegatti et al., (2020) was quite safe and tolerable in terms of side effects. Also, the mild or moderate side effects reported were similar to other vaccines of the same adenovirus vector ChAdOx1 or to other closely related adenoviruses such as ChAdOx2, ChAd3 and ChAd63 at the same dose level (Ewer,2016;Bliss,2018;Folegatti,2019,2020). The reason for choosing a single dose of 5x1010 viral particles was based on the previous MERS-CoV epidemic in which a dose-response relationship was observed (Folegatti, 2020) but also because the COVID-19 pandemic spread rapidly so only a higher dose was selected to provide the highest probability of rapidly inducing neutralizing antibodies. However, because a high dose may be more reactive than two moderate viral load doses, the use of paracetamol is recommended, which has a protective role and can reduce short-lived vaccine-related symptoms without compromising immunogenicity. At the same time, this study showed that T cell responses are very important in the treatment of COVID-19, which was detected by asymptomatic carriers of the virus who showed strong memory T cell responses (Grifoni, 2020; Sekine, 2020; Weiskopf, 2020). Adenovirus vector vaccines are known to elicit a strong cellular response and the ChAdOx1 nCoV-19 vaccine resulted in marked increases in T-cell responses to the SARS-CoV-2 spike as early as day 7, peaking on day 14 and were maintained until day 56 as expected by adenoviral vectors. However, no increase in cellular responses was observed after the ChAdOx1 nCoV-19 boost dose. This is consistent with previous findings regarding viral vector vaccines administered as part of a homologous first aid regimen (Bliss, 2018). The findings of this study cannot be generalized because the number of participants was not high enough and included only 18-55 year olds and healthy volunteers, as it was one of the first phase I trials from which seniors and subjects were excluded diseases that are very important factors in approving the COVID-19 vaccine as these groups are at the highest risk. However, it was the beginning of further testing of the next phases with more age groups and nationally and geographically different populations.

The results of another clinical trial by Polack et al., (2020) for Pfizer BNT162b2 vaccine showed that two-dose planning (30 μg per dose over 21 days) was 95% effective against COVID-19 and had a high profile security. These results also meet the FDA's pre-defined criteria for vaccine approval. The efficacy observed after the first dose was 52% and 7 days after the second dose was 91%. Also, of the 10 cases of COVID-19 observed during the study, only one belonged to the real vaccine group and the other 9 to the placebo group, which proves its high efficacy. Regarding the safety of the vaccine, the same picture was confirmed as in clinical phase 1, i.e. the reactivity was mild or moderate and the reactions were less frequent and milder in the elderly than in younger people. Also, systemic reactivity was more common and severe after the second dose than after the first dose, although local reactivity was similar after the two doses. Severe fatigue was observed in approximately 4% of BNT162b2 recipients, which is higher than that observed in recipients of certain vaccines recommended for older adults (Cowling, 2020). This rate of severe fatigue is also lower than that seen in recipients of another approved vaccine virus for older adults. Overall, the adverse reactions that occurred were transient and resolved within two days of onset. Lymphadenopathy, which generally resolved within 10 days, may have resulted from a strong vaccine-induced immune response. The incidence of serious adverse reactions was similar in the vaccine and placebo groups (0.6% and 0.5%, respectively). This study has some limitations such as not including all vulnerable groups such as pregnant women, immunocompromised individuals or all age groups such as children less than 12 years of age for who further clinical trials will be performed. Finally, the design of the study included the monitoring of volunteers for 2 consecutive years after their vaccination, but this is not possible from a practical and ethical point of view, especially for the placebo group that will not have active immunization for COVID-19. The long-term safety and efficacy evaluation for this vaccine will be performed but not under the close supervision of a placebo group for 2 consecutive years. However, the mRNA vaccine can be a very promising idea for protecting people from other viruses and infectious diseases, as its design and implementation took less than 11 months.

The literature review showed that among the BNT162b1 vaccines encoding the host binding region

(RBD) on the SARS-COV-2 protein coast responsible for ACE2 and BNT162b2 enzyme host binding is the second most appropriate 30μg dose for people aged 18-85 years (Walsh, 2020). However, clinical trials by Sahin U et al., 2020 and Mulligan et al., 2020 showed that BNT162b1 at doses of 10 μg or 30 μg were many subsystems for ages 18-55 years. What prompted the researchers to promote BNT162b2 was its milder reactivity profile in older people, but it showed the same immunogenicity as BNT162b1. The reason for the lower reactivity of BNT162b2 than BNT162b1 is uncertain, as the two vaccine candidates share the same modRNA platform, the same RNA production and purification processes, and the synthesis of lipid nanoparticles. They differ in the nucleotide sequences encoding the vaccine antigens and in the total size of the RNA produced, which results in a number of RNA molecules at 30 μg BNT162b1 which is about 5 times higher than at 30 μg of BNT162b2. RNA nucleotide synthesis has been reported according to research by Kondili et al., 2016, to affect immunostimulatory activity and reactivity profile, and this is a possible explanation for the differences in these vaccine candidates. In terms of short-lived reductions in lymphocyte count after vaccination, they had no relevant clinical effect, were observed in all age groups and probably reflect a temporary redistribution of lymphocytes from the bloodstream to the lymphoid tissues as a functional response to the stimulatory vaccine. This is evidenced by the clinical study of Regules et al., 2017 for the Ebola vaccine. The balance between the immunogenicity and the reactivity of the vaccine at this low dose level of 30μg is important. These results are similar to those of another study against pandemic H10N8 and H7N9 influenza viruses (Feldman, 2019). Immunogenicity was also observed to decrease with increasing age, something that has been observed in other vaccines (Munoz, 2009). Nevertheless, in the elderly participants, a high efficiency of the vaccine was observed, which was further enhanced with the second dose. However, this clinical study has several limitations such as the fact that the importance of the humoral and cellular response to Covid-19 protection has not yet been associated. Also, the clinical phase I of this study showed incomplete results so no statistical comparisons can be made. Finally, participants in this early-stage clinical trial were healthy and had limited racial and intrinsic diversity compared to the general population. In future studies, however, these limitations will be avoided in order to reach a more valid conclusion about the safety and efficacy of this vaccine.

A systematic study by Baden L et al. (2021) found that the efficacy of mRNA-1273 vaccine in preventing symptomatic SARS-CoV-2 infection is higher than that seen for respiratory virus vaccines such as inactivated vaccine influenza versus symptomatic, virologically confirmed disease in adults, for which studies have shown a cumulative efficacy of 59% (Osterholm, 2012). This high apparent efficacy of mRNA-1273 is based on short-term data, and the efficacy of efficacy over time has been demonstrated in other vaccines such as the influenza virus (Ferdinands, 2012). The efficacy of this mRNA vaccine is similar to that of Pfizer BNT162b2 as shown in other studies (Polack, 2020). In terms of safety, it has been found that the reactivity induced by immunization is similar to that recorded in clinical phase I of the same vaccine (Jackson, 2020; Anderson 2020). Overall, local reactions to the vaccine were mild. However, moderate to severe systemic side effects, such as fatigue, myalgia, arthralgia, and headache, were observed in approximately 50% of mRNA-1273 group participants after the second dose. These side effects were transient, starting about 15 hours after vaccination, and subsided in most participants by the second day. However, the degree of reactivity after one dose of mRNA-1273 was lower than that observed for the newly approved recombinant zoster vaccine for people 70 years of age and older and after the second dose of mRNA-1273 was similar to that of the zoster vaccine (Lal , 2015; Cunningham, 2016). Frequent delayed reactions at the injection site were not recorded and the overall side effects up to 28 days after vaccination were similar between real and placebo. At the same time, there were no rare hypersensitivity, but this may be due to to the fact that the sample size of volunteers was not too high to show such a case. The recording of Bell's palsy in this test and in the BNT162b2 vaccine test raises concerns that it may be more than a coincidence and has the potential to be closely monitored (Polack, 2020). It is also worth noting that the mRNA-1273 vaccine did not show any hypersensitivity in the lungs of individuals to cause respiratory disease after vaccination as observed in animal models used for the SARS and MERS-COV vaccine (Tseng, 2012). ; Agrawal, 2016). Key data limitations are the short duration of safety

and effectiveness monitoring. The test is in progress and a monitoring period of 2 years is planned, with possible changes in its design, due to the continuous data collection. Another limitation is the exclusion of pregnant women and children that will be investigated in later studies. Finally, it cannot yet be assessed whether the vaccine inhibits asymptomatic infection as it appears to inhibit symptomatic as there are insufficient data.

Suggestions

According to the above data, it seems that the solution to the pandemic will come from the vaccination of all the populations of the countries of the world. Many vaccines have been found in addition to those analyzed and this is a good thing because many different companies are working on public health to provide the required number of vaccines each time. Of course, science is something that evolves daily and from minute to minute so it is understood that the above literature review can be considered to reflect the data a few months ago instead of today as vaccinations have already started systematically and the clinical phases have been completed. However, it is of the utmost importance for every citizen to realize that vaccines invented thanks to advanced technology and the continuous and uninterrupted studies of scientists, are intended to protect humans and not to harm them. Therefore, every conscious citizen should be vaccinated because no drug has been found against COVID-19 yet and therefore prevention and observance of protection measures are the only "weapons" that exist so far to return to "normalcy".

Conclusions

In conclusion, from the above literature review aimed at evaluating the safety and efficacy of Pfizer, Moderna and AstraZeneca vaccines, it appeared that all three had satisfactory results in the most vulnerable groups of the population who are at the highest risk and approved vaccines should definitely protect them. In fact, all the vaccines showed that the side effects were milder in the elderly than in younger people and the immunogenicity was almost the same in all age groups. Comparing all 3 vaccines with each other, it was found that the Pfizer vaccine, namely BNT162b2 at a dose of 30 μg, was the most effective of all (95%) and caused the fewest side effects in the elderly that are considered a priority for the approval of a vaccine. However, in some of the clinical trials analyzed, it was found that further study and evaluation of the results was necessary because the study may have had some limitations from the beginning, such as not including nationalities from many different parts of the world or involving several vulnerable groups. Of course, as it has been mentioned, the additional studies of the vaccines have already been done in a high percentage of volunteers from all over the world, which is why the regular vaccination has started from January 2021. Finally, the vaccination rate of the general population today in Greece is only 54.9% (data.gov., 2021) and this is mainly due to vaccine deniers who do not stop putting their lives and those around them at high risk.

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