Two urgent needs in the battle against COVID-19: a classic-type vaccine and specific medication

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Abstract: The COVID-19 pandemic has led to the development of vaccines against the causative virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The need for urgent release of anti-SARS-CoV-2 tools has motivated the approval of a new vaccines never used before for mass vaccination, some based on RNA (mRNA vaccines) and some using an adenoviral vector (AV vaccines). Despite high nominal efficacy, in some populations the actual numbers seem to be lower due to several factors that include new viral variants that escape from the immunological response elicited by the vaccines, which have led to new pandemic waves. In fact, the proportion of new cases has decreased in Countries using a classic-type vaccine (inactivated), CoronaVac. In the current August 2021 scenario there is a need to prevent infection, transmission and to diminish the symptoms of the disease by drug repurposing and/or development of ad hoc medication. This manuscript has two aims. On the one hand, it highlights the need to develop classic-type vaccines and to approve them in the US and in Europe. Without classic-type vaccines, herd immunity is unlikely to be achieved. On the other hand, the paper comments on different therapeutic approaches to reduce the severity of COVID-19 and the number of deaths.

Keywords: Vaccine booster, CoronaVac; Sputnik V; adenovirus; RNA vaccines; renin-angiotensin system; viral proteases.

Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been the worst pandemic since the so-called Spanish flu in 1918. The number of deaths and affected people around the world, in only two years, is incredibly high and the return to normal life is not expected anytime soon. As of today (August 10, 2021; <https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---10-August-2021>) the number of affected people is estimated to be >150 million and >3.5 million deaths, often with >10,000 occurring in a single day.

There is no approved drug/intervention to specifically fight the virus once a person is infected. Antibodies extracted from recovered or convalescent individuals may be useful (1–3), although there are doubts about their general efficacy and/or the correct protocol for use (4). Therefore, the first line of defense to stop pandemics is mass vaccination. The success in the fight against the coronavirus is based, mainly, on the speed with which the different vaccines have been developed, approved and produced. Vaccines aim to develop immunological mechanisms to stop infection, disease transmission and/or the worst consequences of infection. This is accomplished by challenging the immunological system with antigens made up of viral proteins. In the fight against SARS-CoV-2, the most successful option has been to combine new-technology vaccines including part of the nucleotide sequence coding for the spike protein. This makes sense, as the

spike is the protein that interacts with the main SARS-CoV-2 receptor on the target cell, namely angiotensin converting enzyme 2 (ACE2).

The production of the spike protein to be directly used in a vaccine is not an easy task. In fact, the spike S proteins of coronaviruses contain from 1104 to 1273 amino acids (5). Rapidly producing the huge amounts needed for the worldwide vaccination of hundreds, even thousands, of millions of people is a challenge that was never undertaken. An alternative option is to make the vaccine with a nucleic acid that encodes for the protein (in whole or in part). While it is difficult to produce and purify the protein *in vitro*, thus keeping its natural conformation and antigenicity, it is more feasible to produce the nucleic acids that encode for the protein. This approach has therefore been adopted with success in terms of efficacy against infection and production speed. Two types of nucleic acids have been used: RNA and DNA. In mRNA vaccines, the coding sequence is in the form of messenger RNA (mRNA), which enters the cells of vaccinated individuals and can be easily converted into the spike protein. To deliver the mRNA to the cells, a lipid-based encapsulation/nanoparticle can be used. In DNA vaccines, the DNA coding sequence for the spike protein can be delivered with viral vectors, like for instance those based on adenovirus (AV), which is a non-enveloped DNA virus. AVs were being developed as vaccines for diseases such as Ebola (6), but the COVID-19 pandemic has shifted the focus to the production and approval for emergency use of AV vaccines against SARS-CoV-2.

In terms of current vaccines using sequences coding for the spike protein and being administered worldwide, Pfizer and Moderna vaccines are based on RNA, whereas AstraZeneca, Johnson & Johnson and Sputnik V vaccines are based on AV, i.e. on DNA. At present (August 10) the ones approved in the European Union are those from Pfizer, Moderna, AstraZeneca, and Johnson & Johnson. In the United States, all except the AstraZeneca vaccine have obtained emergency use authorization. In other countries the vaccine developed in Russia, Sputnik V, is being tested with supposedly high efficacy rates and there are still doubts on its approval in the European Union. In China and some countries in South America, a classic type vaccine is the one that is mainly used. Looking at the whole picture one does not understand why in the EU and in the US no classic-type vaccine has been developed and approved by regulatory bodies. For decades classic-type vaccines have been developed using methods that have been successful in fighting a variety of diseases (7,8). Since the pioneering work of Louis Pasteur developing a vaccine against the rabies virus (See (9)), they have proven effective in the prevention of serious diseases caused by viruses (see WHO global vaccine Action plan: <https://www.who.int/teams/immunization-vaccines-and-biologicals/strategies/global-vaccine-action-plan>; accessed on August 16, 2021).

Benefits versus risks associated to new vaccines

First and foremost, the new mRNA and AV vaccines developed to fight COVID-19 are generally safe, at least in the short-term. However, due to the urgency to stop spreading SARS-CoV-2, they have been approved in less than one year after the outbreak of the SARS-CoV-2 pandemic. For one thing, possible long-term problems of vaccinated people due to a specific vaccine have not been empirically addressed. Even though, considering the preexistent bibliography, these effects are very unlikely to happen, this issue cannot be ignored considering the huge number of people receiving these vaccines. On the other hand, urgency has prevented the appearance of classic vaccines, which have shown in the past an impeccable efficacy and safety record (10,11). Accordingly, although mRNA/AV vaccines may be instrumental to achieving large numbers of short-term vaccinated people around the world, classic-type vaccines must also be considered. By August 2021, there are two classic-type vaccines approved for human use; both have been developed in China: Covilo or BBIBP-CorV (from Sinopharm) and CoronaVac (from Sinovac Research and Development) ([https://www.who.int/es/news-room/q-a-detail/coronavirus-disease-\(covid-19\)-vaccines](https://www.who.int/es/news-room/q-a-detail/coronavirus-disease-(covid-19)-vaccines); accessed on August 16, 2021).

Despite the obvious benefits of reducing infections and deaths in vaccinated people, the risks must be brought to the table. The risks of thrombi for humans receiving the AstraZeneca or Johnson & Johnson vaccines are serious, but can be weighed against the risk-benefit assessment. Due to the high number of variables, it is difficult to reliably compare the percentage of cases with thrombus versus the total number of vaccinations with the overall risk of death in unvaccinated people. But it is reasonable to accept that the relatively low number of cases with thrombosis should not stop vaccination with AstraZeneca or Johnson & Johnson vaccines. However, caution should be exercised when these vaccines are administered to people taking medications in which one of the potential side effects is thrombus formation; the most obvious case is certain types of birth control pills. Another risk of the mRNA/AV vaccines is the possibility of integration of exogenous material into the DNA of host cells (12). AVs have been tested for decades as vectors in gene therapy and the problems of their use have led to the development of safer vectors such as adeno-associated viruses (see (13) for review).

The risk is seemingly lower in the case of mRNA vaccines, but it has been demonstrated that genetic material of SARS-CoV-2 can be converted into DNA that integrates into the human genome (12,14). The human genome does not include the gene for any typical reverse transcriptase, but it includes retrotransposons that can “move” using a copy and paste mechanism that requires a RNA intermediate. Accordingly, retrotransposon may act as instruments to convert RNA from viruses or mRNA vaccines into genomic DNA (12,14). One of the deciphered mechanisms is mediated by the LINE-1 retrotransposable element ORF2 protein (15,16). The human genome contains several full or truncated sequences of long interspersed element-1 retrotransposons and it is assumed that >80 of those elements can be transcribed; random integration of elements in the genome has been related to a variety of diseases (15,17,18). Interestingly, SARS-CoV-2 infection alters the usual dynamics of some transposable elements, such as LINES, increasing their expression and, therefore, the probability of insertion of new transposable elements (19). Additionally, SARS-CoV-2 is not the only RNA virus with positive polarity (that is, that is directly transcribed by the host cell ribosomes) that has the capability of directly interacting retrotransposons; among others, Hepatitis C (16) or Sindbis (20) viruses may interact with transposons. In summary, the integration of exogenous genetic material into host genome may lead to risks, such as premature cell death or tumor cell growth, that cannot be addressed in the short term, i.e. before emergence use anti-COVID-19 vaccine approval.

The efficacy issue

The efficacy of a vaccine is not a direct measure of its capacity to avoid the symptoms of the COVID-19. In the case of the vaccines, efficacy cannot be measured as in the case of a drug for a disease, from diabetes to Alzheimer's. Efficacy of antidiabetic medication is measured in patients that take the drug and after some period of time the reduction in plasma glucose levels are measured. Few clinical parameters are needed, just the glycemia and the percentage of reduction that is considered as end point. If a 20% is selected, the efficacy is measured by the number of patients whose levels are reduced by more than 20% versus the total number of patients. In Alzheimer's disease the end point consists of increasing the score in a cognition test, for instance the mini-mental test (MMSE: Mini-Mental State Examination). The main parameters needed to test any anti-dementia medication are to select the range of scores of patients to recruit and to select the minimum expected score increase in the MMSE scale.

More parameters plus some ad hoc assumptions are needed for efficacy assessment of vaccines. First and foremost, vaccinated people does not have any disease. Then, it is not possible to assess efficacy by directly looking at whether or not vaccinated people have been cured or have fewer symptoms of the disease. The first assumption is that vaccinated individuals will have similar exposure to SARS-CoV-2 than non-vaccinated individuals (or placebo inoculated individuals). Fortunately, an ad hoc surrogate marker for vaccine efficacy is the level of IgGs in plasma, mainly

of neutralizing antibodies, i.e. antibodies that prevent infection. Unfortunately, in SARS-CoV-2 it is important to know the level of the IgGs but also the composition of IgGs. The serological quick tests have demonstrated that different COVID-19-suffering individuals produce different antibodies. In other words, quick tests, which nominally have >90% sensitivity, lead to false negatives, i.e. sensitivity may be >90% in one given infected population and may be far lower in another infected population. Plasma from convalescent patients show a mixture of anti-SARS-CoV-2 antibodies (21). Microfluidic devices have shown that humoral responses to coronavirus can elicit with a variety of antigen / antibody interaction affinities (22). To make things even more complicated, many of the vaccination schedules include two shots and this adds complexity to the estimation of the real preventive effect of anti-COVID vaccines. Taken together, it is almost impossible to estimate the efficacy of any vaccine with reliability. In addition, the neutralizing antibodies, i.e. those that impede infection, are unknown and/or may be neutralizing for a given strain of the virus but not for a different one. In practical terms, only the big pharma has the potential to enroll thousand individuals and to provide an efficacy estimates to apply for approval by regulatory bodies. Also, the efficacy data may vary from trial to trial, and or by adding more data if the trial is extended. It has been common for the companies developing the mRNA/AV vaccines to present, upon time, increases in the percentage of efficacy for the same vaccine. The poor efficacy values of classic-type is surely behind the decision to stop the development of some vaccines such as the TMV-083 (previously known as MV-SARS-CoV-2), which was developed by one of the most experienced institutes in the World, the Pasteur Institute (23) (see <https://www.pasteur.fr/en/all-sars-cov-2-covid-19-institut-pasteur/research-projects/covid-19-vaccine-against-sars-cov-2-infection-using-measles-vector>; accessed on April 19, 2021) and its partner company: Sanofi.

In summary, mRNA/AV vaccines have prevented deaths, but they have not been able to stop the spread of the virus and have favored the appearance of new variants. It is essential to have vaccines that not only prevent death, but also stop transmission and genetic shift/drift. In addition a very recent paper reporting clinical research with individuals vaccinated with RNA vaccines states: *“we document significant declines in antibody levels three months post-vaccination, and reduced neutralization of emerging variants”* (24).

The third dose issue

The use of vaccines that are not able to stop the transmission has contributed to selection of viruses with mutated forms of the spike protein. This issue was, among others, raised by Nobel Laureate Luc Montagnier. He doubted that vaccination to stop COVID-19 spread was convenient due to the appearance of new variants. No doubt vaccination has been instrumental to decrease the death toll, but novel SARS-CoV-2 variants have arisen that are able to lead to COVID-19 symptoms in vaccinated people. The current pandemic is due to a virus with a high transmission capacity, which means that a given individual may be exposed to the virus more than once and in relatively short periods of time. It is often forgotten that all people, vaccinated or not, may be infected by any SARS-CoV-2 variant. But mRNA/AV vaccines that use the sequence (DNA or RNA) of a given spike protein, may not be efficacious in attenuation infection/symptoms produced by new variants. In fact, more and more vaccinated people are being re-infected and able to infect close contacts. For instance, the AstraZeneca vaccine (ChAdOx1 nCoV-19) has shown a highly reduced efficacy, among others, against the B.1.351 variant. In summary, mRNA/AV vaccines have been useful but have led to new variants in a selection-escape fashion. In the search for convincing data to obtain vaccine approval, clinical trials with two injections were designed (with the exception of the Janssen vaccine). On the one hand, two shots surely lead to a higher production of anti-spike antibodies in serum and this may be convincing for regulatory bodies. On the other hand, two shots may be needed and/or convenient for viruses that do not have high mutation rates. However, two shots to combat a virus RNA that mutates

so rapidly is, quite likely, not the best option. Worse, here are chances of approval of a third shot of the same vaccine. Taken together, all available information and basic knowledge of the human immune system, indicates that a third dose with the same vaccine is not the best option. Fortunately, there is an alternative that, importantly, has already proven with high success, namely the use of a classic-type vaccine. By previous knowledge with this type of vaccines, the selection of new variants would be minimal and, in addition, “classical” vaccines lead to more efficient immunological tools, humoral and cellular, to fight SARS-CoV-2 via diverse components and not only via the spike protein.

Vaccination that allows viral escape by mutation will compromise the control of pandemics and the achievement of herd immunity. In reality, countries that are using mRNA/AV vaccines anticipate that herd immunity will not be achieved in such a scenario, complementary approaches should be sought (25). To combat the escape of the human immunodeficiency virus (HIV) by mutation, the so-called Highly Active Antiretroviral (HAART) or “triple” therapy was developed for acquired immunodeficiency syndrome (AIDS) patients. While one single drug was not efficacious to control the disease, the combination of three different compounds prevented mutations thus allowing disease control. The triple therapy consisted of inhibitors of two relevant components of HIV-1, the reverse transcriptase and the main viral protease (26,27). AIDS is now considered a chronic disease that produces few direct deaths. Currently, it is not possible to prevent the escape of SARS-CoV-2 by mutation using drugs, but the availability of different types of vaccines opens a window of opportunity. In the same way that a single drug is not effective for AIDS patients, a single vaccine can reduce the number of deaths, but it can allow a viral escape by mutation, a reduction in the effectiveness of the vaccine and an inability to achieve herd immunity. Accordingly, more shots of the very same vaccine will have a limited benefit in comparison with shots of a heterologous vaccine (28,29). More shots of the same vaccine may be detrimental on putting pressure to the virus thus selecting more infective viral particles. Recent developments in the anti-HIV-1 research field include the use of combining vaccines that, to combat the HIV-1 pandemic “*must induce responses capable of controlling vast HIV-1 variants circulating in the population as well as those evolved in each individual following transmission*” (30). In summary, despite the lack of a drug cocktail, a combination of different vaccines is emerging as a real alternative to effectively combat SARS-CoV-2. Obviously, the optimal treatment would not be to use vaccines directed against the same protein, that is, the SARS-CoV-2 spike protein. In European countries and in the US, all vaccines are directed against the spike protein. Should these countries approve vaccines of a different type (non-RNA-based, non AV-based) and/or directed against other viral components?

New cases after 30% population vaccination using new- or classic-type vaccines

Available data suggests that reinfection and collapse of emergency units at hospitals may occur in countries using the mRNA/AV vaccines even though the percentage of vaccinated population is high (31,32). Perhaps the main example is Israel that was among the quickest in vaccinating with mRNA/AV vaccines. The same trend, i.e. new waves after massive vaccination with mRNA/AV vaccines, has occurred in various European Countries and in the US. This trend is opposite in the only three countries that used the CoronaVac vaccine as the main vaccine (Figure 1).

Figure 1 shows the trend of new cases in three Countries mainly using CoronaVac and in three Countries using mRNA/AV vaccines. Despite alarms in Uruguay, it is clear that increasing the percentage of population vaccination with CoronaVac has led to a dramatic decrease in the proportion of new cases. Something similar has occurred in another Country mainly using CoronaVac, Chile. The data available for China suggests an increase followed by a sharp decrease, but it should be noted that neither the rises nor the falls are significant as total 2021 cases, measured per 1,000,000 inhabitants, are negligible in China compared to the other selected countries (5 in China versus 65,543 in Israel or 53,200 in the US, date: August

25). In sharp contrast, France, Israel and the US shows an increase of new cases upon increased vaccination using mRNA/AV vaccines.

Figure 1. New COVID-19 cases versus percentage of vaccinated population. Data (retrieved until August 24, 2021) have been selected using 30% vaccinated population as threshold. Chile, Uruguay and China have mainly used CoronaVac vaccine. France, Israel and the US have used only mRNA/AV vaccines. The numbers below the name of the Country indicate total reported cases from the beginning of 2021. For comparison purposes the same axis, X and Y, were used in all graphics. A file with the data used construct the graphics, coming from repositories containing official data reported by the Countries (see “Data availability statement” below).

For statistical analysis we have considered 10 countries (US, Israel, Greece, Portugal, Ireland, Italy, Spain, United Kingdom, Denmark and France) that have not used CoronaVac but mRNA/AV vaccines, and the only three countries using CoronaVac as the main vaccine (>70% administrated doses at date August 24, 2021), China, Chile and Uruguay. Data were retrieved from a big data source, Github (<https://github.com/owid/covid-19-data/tree/master/public/data>), which is forged with COVID-19-related data in official webs such as in the Oxford COVID-19 Government Response Tracker or in independent global health research centers such as the Institute for Health Metrics and Evaluation at the University of Washington. The Excel file containing all data was directly downloaded from Github (<https://covid.ourworldindata.org/data/owid-covid-data.xlsx>; accessed (on August 24, 2021; see “Data availability statement” below). The interaction graphic was obtained using Statgraphics v. 18.1.14 from a general linear model analysis with type of vaccine (mRNA/AV or CoronaVac) as a qualitative factor, % vaccinated population as a quantitative factor and, as a dependent variable, the relative % positives in 2021 (which is the relation of new positives after reaching 30% of the vaccinated population and the total positives in 2021). The 30% threshold was set up because a lower percentage of vaccination has little effect on pandemic indicators). Although vaccination began at the end of 2020 and the beginning of 2021, only data from 2021 were analyzed. To avoid interference due to differential public health decisions and differences in the timing and rate of vaccination in each country, no attempt was made to make comparisons between countries using similar vaccines. We have found a very significant correlation between the percentage of population receiving the mRNA/AV vaccination (full regime; two shots except for the Johnson & Johnson vaccine, which is administered in only one shot) and number of new cases after reaching 30% vaccination of the population in a given Country, namely cases in 2021 after reaching 30% vaccination versus total cases in 2021. The two lines (one for mRNA/AV viruses and another for CoronaVac) are of opposite slope, i.e. correlations are opposite when considering CoronaVac or the vaccines based in mRNA/AV. Whereas the ratio of cases after 30% vaccination increases with further vaccination with mRNA/AV vaccines, the ratio decreases in countries where CoronaVac

is used. In fact, statistical analysis shows significance for a differential trend using CoronaVac or mRNA/AV vaccines. The correlation was done using proportion of cases as quantitative variable and type of vaccine as qualitative variable. The significance holds if only three countries using the mRNA/AV vaccines are considered, i.e. considering data from 3 countries in both sets of data. The significance also holds taking out the data from China, whose management of the pandemic has been quite different to that in many other countries.

In summary, vaccination with mRNA/AV vaccines does not stop transmission, while in countries that use the CoronaVac vaccine, cases decrease with increasing population vaccination rate, suggesting effective neutralization that may eventually lead to herd immunity.

The need of a classic-type vaccine

A complete schedule of a mRNA/AV vaccine, two doses of Pfizer, Moderna or AstraZeneca, and one dose of the Johnson & Johnson vaccine, as many organizations define including The Pan American Health Organization/ World Health Organization (https://ais.paho.org/imm/IM_DosisAdmin-Vacunacion.asp), in 50% of the population has not eradicated the virus and, worse, new waves of infections have appeared. In our Country (Spain) we were, at the end of July 2021, in the mid of the fifth wave and there are officials stating (August 20) that the sixth wave is coming. In elderly houses in Catalonia (Spain) in which all residents are vaccinated (>90% with mRNA vaccines) there is a surge of new cases (August 2021; official data in: https://dadescovid.cat/?drop_es_residencia=1). This was not expected when vaccination started. Some of the reasons of having such unexpected scenario may be now figured out.

On the one hand, and apart from the reduction upon time of the antibody levels (*see above*; **The efficacy issue** section), it is known that significant amounts of mucosal IgA is associated with less viral transmission. Likewise, in all the viral infections studied to date, a higher proportion of IgA at the epithelial level reduces the risk of re-infection (33). Therefore, the production of IgAs is important to reduce (upon vaccination) re-infection and associated transmissibility (34). Not all vaccines have confirmed production of IgAs at the mucosal level; a recent publication reports IgAs secretion to human milk after shots of Pfizer's vaccine (35). This finding is important for preventing infection of the neonate, but the relevance in epidemiological terms is under question. Efficacious prevention of the infection requires production of aggregated, secretory, forms of IgA (SIgA), whose affinity for antigens is much higher than monomeric IgA (36). Therefore, one indicator of the effectiveness of a vaccine is the number of mucosal SIgAs and whether they are neutralizing or not (36). The few studies on this matter suggest that IgA production by mRNA/AV vaccines is, at the very least, very modest (37), and this seems to be one of the reason of low efficacy in reducing infection and transmission despite the high nominal values of efficacy in producing antibodies (33).

On the other hand, although it is commonly thought that the only antibodies capable of preventing infection are neutralizing antibodies, non-neutralizing antibodies are important irrespective of their later involvement in the viral replication cycle (38). In this sense, classic-type vaccines lead, by definition, to a more qualitative diverse repertoire of neutralizing and non-neutralizing antibodies than vaccines only based in producing IgG against a single viral protein.

The CoronaVac vaccine, developed by a Chinese company, Sinovac Research and Development, consists of inactivated SARS-CoV-2 and aluminum hydroxide as adjuvant. It has been among the first vaccines to be developed and at present is being tested in different countries (39). Only in China 1 million people was already vaccinated by the end of 2020 in a phase III clinical trial that started in November 2020. Fewer data about CoronaVac are available in English if compared with the huge amount of information available (in English) for the other vaccines. Although a direct comparison between classic-type vaccine and mRNA/AV vaccines is difficult to perform, some

reviews on this theme have recently appeared (see, for instance (39–41)). A recent paper compares data from 13 clinical trials of 11 different vaccines, taken both reports in English and in Chinese. The conclusion of the authors is that: *“Most of the COVID-19 vaccines appear to be effective and safe. Double-dose vaccination is recommended. However, more research is needed to investigate the long-term efficacy and safety of the vaccines and the influence of dose, age, and production process on the protective efficacy”* (42).

It is remarkable and far from being generally known by the population and by Western Health authorities that, CoronaVac lacks the serious side effects identified for RNA- and AV vaccines (43), namely, clot formation, Guillain-Barré syndrome, myocarditis, etc. Additionally, vaccine developers already have experience on controlling pandemics with inactivated vaccines, such as that caused by the poliovirus at the beginning of the 20th century, whose mutation rate is similar to that of SARS-CoV-2 (44,45) and whose basic reproduction number (R_0) throughout the pandemic was not different from that of the coronavirus (46,47). In summary, mRNA/AV vaccines have instrumental for the quickness in being approved and for the high nominal efficacy rate but classic-type vaccines are needed and the only one already developed shows that it should enter into the vaccination program to combat COVID-19 in all over the World.

Safety, tolerability and immunogenicity was successfully addressed in a first phase I/II trial in volunteers of the Suining County of Chinese Jiangsu province. One of the outputs of the study was the selection of 3 µg CoronaVac dose for phase III trials, which have been performed in different countries. Approval has been granted already in, among others, China (48), Brazil (<https://www.reuters.com/article/us-health-coronavirus-brazil-coronavac-idUSKBN29R2GL>; accessed April 23, 2021), Uruguay and Chile (<https://www.ispch.cl/noticia/isp-autorizo-la-vacuna-coronavac-del-laboratorio-sinovac-life-sciences-co-ltd-para-uso-de-emergencia-en-el-pais/>; accessed April 23, 2021).

Chile, which is a country of reference in anti-COVID-19 vaccination, is using the CoronaVac and the Pfizer vaccines in a 80:20 approximate proportion (80 CoronaVac, 20 Pfizer); the two vaccines are scheduled to be given as two injections. CoronaVac was approved in Chile after the results of a phase III clinical trials performed in the Country. It has been noticed that the efficacy in preventing productive infection, especially after the first shot is modest and comparable to that whose development was stopped by Pasteur/Sanofi, i.e. in the 50-60% range. Remarkably, this low level of efficacy does not result in poor performance and this has been proved by data obtained upon continuing vaccination schedules. The good COVID-19 data in Chile, which is due to the Pfizer and CoronaVac vaccines, strongly suggest that efficacy estimates are not enough to rule out a vaccine. There is strong evidence showing that despite low efficacy estimates, CoronaVac is achieving the key objective, which is to save human lives. Another phase III trial (PROFISCOV Study) was conducted between July 21 and December 16, 2020 in Brazil among healthcare professionals (49,50). The conclusion as posted in Elsevier’s SSRN database is that the vaccine was *“efficacious against any symptomatic SARS-CoV-2 infections and highly protective against moderate and severe COVID-19”* (50).

Some of the advantages of vaccines that protect from infection despite having low nominal efficacy values and lower antibody titers than those elicited by mRNA/AV vaccines, may come for an appropriate engagement of T cell responses. The likelihood of requiring robust T helper cell responses to prevent COVID-19 infection has been suggested from a mouse study using recombinant spike proteins (51). In fact, based on previous experience with coronavirus, the risk of antibody-dependent potentiation (ADE) for anti-SARS-CoV-2 is significant, pointing to the need to develop vaccines that are less dependent on antibody production and more than T cell responses (52). In summary, both humoral and cellular responses are needed for an effective fight against this specific coronavirus. Surprisingly, there is evidence of negligible impact of SARS-CoV-2 variants on T-cell responses, i.e. variants that escape the action of antibodies are likely unable to cope with CD4⁺ and CD8⁺ T cell reactivity (53). In this sense, CoronaVac apart from

being safe and producing neutralizing antibodies against the receptor binding domain of the S1 spike protein, immunization induced the activation of T cells (when exposed to SARS-CoV-2 antigens) and the secretion of IFN- γ (54). A recent publication shows that one dose of CoronaVac is already effective against the spreading of the P-1 Brazilian variant of the virus (55).

The need of a specific anti-COVID-19 medication

Drugs used at the beginning of the pandemic, including antibiotics and human immunodeficiency virus protease inhibitors, were not at all effective. When noting that the most serious symptom derived from an imbalance in the immune response with exacerbation of the production of pro-inflammatory cytokines that aggravated the pneumonia, the treatment of choice consisted of glucocorticoids. Since vaccines have not been able to fully prevent infection and disease transmission, there is an urgent need to develop specific anti-COVID-19 drugs.

One interesting possibility is to target the renin-angiotensin system (RAS). The rationale is mainly based in the main SARS-CoV-2 receptor, angiotensin converting enzyme 2 (ACE2). This RAS member interacts with other RAS members such as angiotensin II receptors, which belong to the family of G protein-coupled receptors (GPCRs). GPCRs are very druggable and, in fact, are the target of about 40% of approved drugs worldwide. In addition, antagonists of angiotensin receptors are approved to combat hypertension. Accordingly, it would be informative to perform clinical research correlating the RAS status in with disease severity in COVID-19 patients. Parameters to consider are arterial blood pressure values, the use or not of anti-hypertensives and the type of anti-hypertensives, i.e. whether antihypertensives targeting RAS leads to a differential course of the disease compared with using other type of antihypertensives. In addition, targeting RAS members may lead to decrease in infection because RNA viruses need GPCRs to enter into cells and several RAS members are GPCRs and ACE2 interacts with some of those RAS GPCRs (see (56) and references therein). Often, the serious effects of SARS-CoV-2 infection that can eventually lead to death are due to an imbalance of the immune system in which macrophages play a key role (57). A hot topic in the immune system field is to find drugs able to produce M2 macrophages that, opposite to the M1 or proinflammatory macrophages, facilitate the resolution of inflammation. Accordingly, the discovery of targets to produce M2 macrophages is a promising approach to fight against COVID-19.

Soon after the beginning of the pandemics, a laboratory that has been for years involved in coronavirus research solved the structure of the main protease of SARS-CoV-2 (M^{pro} also known as 3CL pro) also designing specific inhibitors of the alpha-ketoamide type (58). These inhibitors are at the forefront of being used as specific anti-COVID-19 tools (59).

All over the world there are screening of several compound libraries to try to find inhibitors of viral infection. At present several target candidates have been proposed to manage SARS-CoV-2 infection but further research is needed to find the most promising ones in terms of druggability, efficacy and safety (60–62).

Data Availability Statement: Data used to build Figure 1 will be available upon request when the paper becomes published (data retrieved from repositories with official data on COVID-19 from all Countries).

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