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Review

Harnessing Antiviral Peptides as Means for SARS-CoV-2 Control

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Abstract: Several times during the past two decades, epidemic viral diseases created global challenges. Although many solutions have been proposed to deal with this tight spot, it is still believed that public vaccination represents the most effective strategy to handle it. So far, various kinds of vaccines including protein subunits, virus-like particles, inactivated, live attenuated, viral vectors, RNA, and DNA vaccines have been used in the prevention of COVID-19. Among the various categories of vaccines, peptide vaccines have created a new hope for quick and trustworthy access due to the development of proteomics equipment. This review specifically focuses on vaccines and peptide therapies in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). We consider here the efficacy and safety of subunit and synthetic peptides vaccine in clinical trial phases. Furthermore, monoclonal antibodies with the ability to suppress the development of SARS-CoV-2, those candidates that have entered into clinical trials until March 2023, were selected and evaluated.

Keywords: SARS-CoV-2; peptide vaccines; methodological processes; COVID-19 vaccination; monoclonal antibodies; clinical trials

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1. Introduction

Looking through the historical lens, every few decades human health has faced epidemic diseases that seriously endanger human life [1]. Viral infection on a population scale is one of the oldest risks that always emerge with new faces. The infections can spread rapidly through the public, particularly in areas with a high population density. The transmission of a virus usually depends on factors, such as the mode of transmission, the virulence of the virus, and the vulnerability of the population. Some viral infections, such as the common cold or flu, are relatively mild and are typically self-limiting. However, other viral infections such as the coronavirus family can be much more severe and may lead to serious health consequences and/or death. When a viral infection spreads through a population, it can quickly lead to an outbreak or epidemic. In some cases, the infection may continue to spread and become a pandemic, affecting populations across multiple countries or continents [1,2].

The SARS-CoV-2 belongs to the *Coronaviridae* family. This is an enveloped positive-stranded RNA (ribonucleic acid) virus, which has the largest viral genome (26–33 kilobases) among the RNA viruses [3]. According to the phylogenetic classification, *Coronavirinae* can be further divided into four groups; alpha, beta, gamma, and delta. This subfamily has been identified to infect mammals and birds, including bats, mice, pigs, dogs, cows, chickens, horses, and humans [4]. Few studies are showing that bats can host many types of coronaviruses, which vary dramatically depending on the living area and the type of bat. It seems that these animals are the natural reservoir of this subfamily.

Human coronaviruses (HCoVs) are related to numerous respiratory diseases of varying severity, including pneumonia and bronchitis. Today, the human coronavirus is known as one of the fastest-changing viruses due to the high speed of genomic nucleotide exchange and recombination [5]. Viruses associated with severe acute respiratory syndrome (SARS) and Middle East acute respiratory syndrome (MERS) are among the types of pathogens related to *Coronavirinae*, which are common between humans and animals and can cause severe respiratory disease in humans [6]. SARS coronavirus (SARS-CoV) first appeared in China in 2002. The outbreak of SARS-CoV lasted for eight months, almost 10 years after the emergence of SARS-CoV (also known as SARS-CoV-1), a highly pathogenic human coronavirus with the name MERS coronavirus (MERS-CoV) appeared in Saudi Arabia. SARS-CoV-2, another type of coronavirus originally named "novel coronavirus" was identified in Wuhan, China in December 2019. Based on the different analyses, the stable mutation in the nonstructural protein 2 (nsp2) has led to SARS-CoV-2 being more contagious than SARS-CoV-1 [7].

SARS-CoV-2 as an RNA virus is genetically located in the beta coronavirus category and uses a glycoprotein (spike protein) to bind to the angiotensin-converting enzyme 2 (ACE2) receptor [8]. Following SARS-CoV-2 infection, some infected people may remain asymptomatic or have only mild symptoms, whereas others develop pneumonia and acute respiratory distress syndrome (ARDS) that require intubation in special care units and often causes complications with unfavorable results. Mortality is associated with age, the presence of underlying (background) diseases, the severity of the disease, increased respiratory failure, a low number of lymphocytes, and previous infection [9]. The transmission of SARS-CoV-2 is through respiratory droplets. According to some studies, the virus may be transferable in some people 5 to 13 days after discharge and partial recovery of the disease; therefore, it is necessary to take precautions for the patients during the recovery phase. As mentioned, ACE2 acts as a receptor for the entry of the SARS-CoV-2 virus [10]. Widespread expression of the receptor in various cells, such as alveolar type II (AT2) cells of the lung, upper esophagus, epithelial cells, absorptive enterocytes of the ileum and large intestine may play a significant role in the infection pathways associated with SARS-CoV-2 virus [11].

Although during the last 30 years, a new coronavirus has affected the public health system every 10 years, these previous viral infections were self-limiting. However, in the case of SARS-CoV-2, the consequences and outputs were much more severe, and despite the predictions made about the spread of the virus. In this regard, the design and production of efficient vaccines, due to the presence of asymptomatic carriers and genetic mutation of viruses are challenging [8,12].

When designing a vaccine, researchers must first have complete information regarding the characteristics of the antigen, adjuvant, vaccine manufacturing, and delivery system. Due to the rapid availability of genomic and structural information on the SARS-CoV-2 virus for researchers, the efficient production of recombinant vaccines was faster than the production of weakened and inactivated live vaccines [13]. Also, the available information on the production of vaccines against SARS/MERS has been helpful for the development of vaccines against SARS-CoV-2. The use of nanotechnology systems has provided great acceleration in the production of new and efficient vaccines and has helped a lot in the development of new vaccines [14].

2. Methodological Routes to Discover and Finalize a Peptide as a Protective Agent

The idea of using peptides to stimulate the immune system has a very long history. However, the entry of this concept into the field of modern medicine is due to the studies of William Bradley Coley (1862–1936). Studies show that the peptides as vaccine candidates against SARS-CoV-2 are generally synthetic [15]. It is expected that the sequence of a peptide vaccine (which is between 20 and 30 amino acids) must be immunogenic or able to disrupt a stage of the virus's path of pathogenesis. When it comes to the synthesis of peptide vaccines, it is expected that their production process will be carried out with higher precision and reproducibility, which will guarantee the quality of vaccination, as well as the speed of their industrialization [16]. However, studies on some of these types of peptides show that due to the not enough strong immune response they create, the presence of adjuvants is always needed to obtain an adequate response [15]. Another challenge that has been observed is their vulnerability to proteases in the body's environment. As a result, most peptide vaccines do not have much resistance against proteases. However, it is suggested that the challenge can be overcome by inserting the vaccines into liposomes, conjugation on the surface of other carrier proteins, or connecting them to the surfaces of nanoparticles [17]. In this section, according to Figure 1, the methodological ways by which peptide vaccines can be proposed are presented.

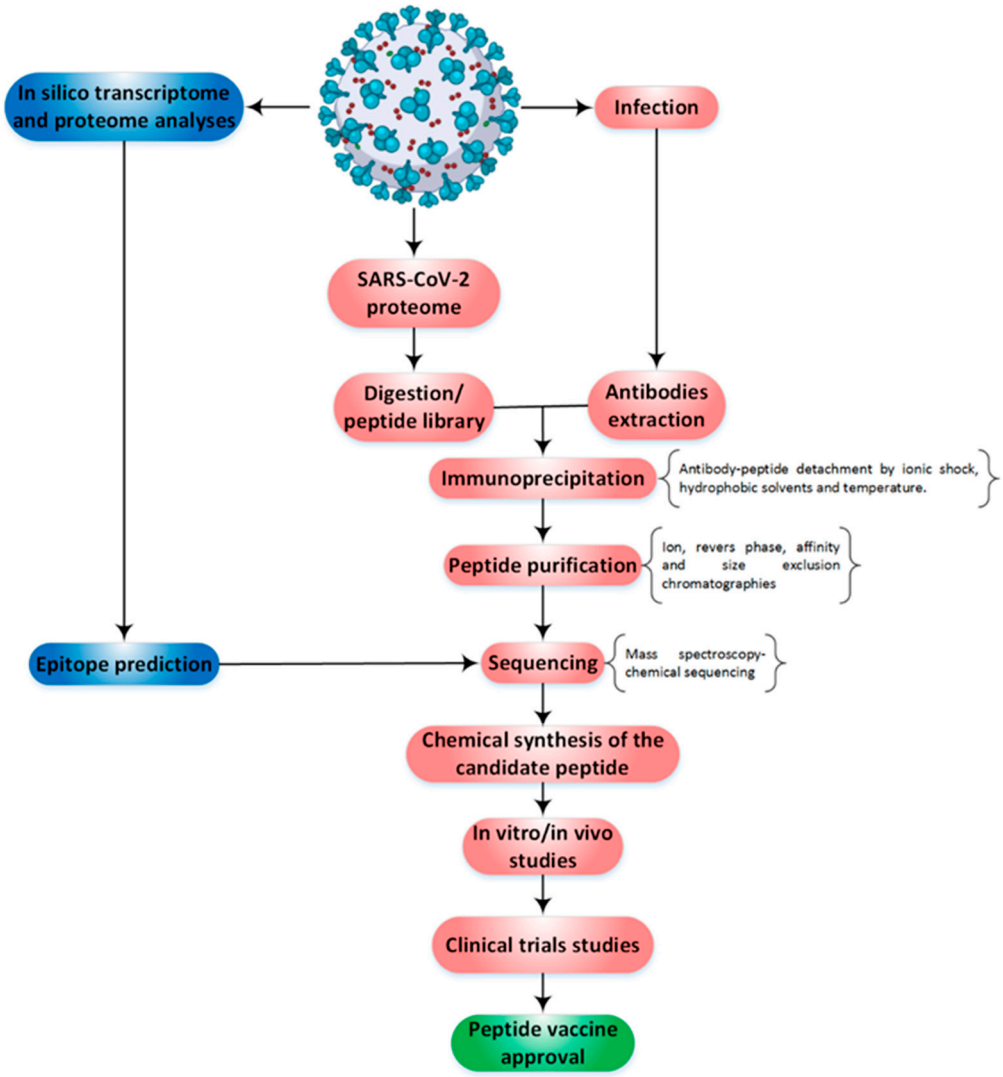

Figure 1. The steps are taken to obtain a final vaccine peptide. The path to reach the peptide vaccine is from either top to bottom or vice versa. In the scheme, in the pink part: first different peptides are

extracted from SARS-CoV-2, and then the final peptide sequence is achieved by performing other steps. In another path (blue), a specific sequence is obtained from the beginning according to the considerations of different in silico studies, and then an attempt is made to confirm the function of the proposed peptide with its chemical synthesis. It is believed that the first path is associated with more effort and higher confidence, while the second path, although the result is less certain, takes less time. Sometimes a mix of both routes is adopted to go through the peptide vaccine approval process.

Depending on the aim of the research, it is possible to extract the proteome of SARS-CoV-2 from the entire viral proteome or a part of the virus structure; e.g., the membrane. For the virus, it has been stated that reverse transcription-polymerase chain reaction is the most useful way to reach the virus genome in infected patients [18]. However, although this path is well explained and implemented, it has dark spots that cast a shadow on the accuracy of the extracted outputs. For example, the presence of some mutations on the path from gene to protein may cause the final prediction of the protein sequence from the gene with a percentage of error [12]. Therefore, although the direct examination of the viral proteome is a time-consuming and long process, the obtained data are more trustable. In general, it has been seen that there are gene sequences for 28 proteins in SARS-CoV, of which only 16 proteins have been structurally characterized [19]. Utilization of the mass spectroscopic techniques in combination with the computer-aided analyses of data allowed for the characterization of the interactions between the known proteome in SARS-CoV-1 and -2 with host cellular proteins and revealed that there are a total of 1484 interactions between them [20,21]. This sequencing process is highly accurate for peptides that are obtained from enzymatic digestion in vitro, however, for peptides that are obtained in antigen-presenting cells (in vivo digestion), it doesn't show high accuracy. As a result, whether the viral proteome originated from antigen-presenting cells or directly prepared from viral enzymatic digestion will be a decisive turn point in the accuracy of the information obtained by mass spectrometry sequencing [21].

After sequencing the final peptide, to ensure the outcomes, the final peptide should be synthesized by recombinant and/or chemical routes according to the length of the sequence and the structural complexity. Usually, due to the number of peptide residues (less than 30 amino acids), chemical synthesis is considered. Then by purifying the synthesized peptide, and performing in vitro and in vivo assays, an attempt will be made to test the excitability of the immune system by the peptide. If the synthesized peptide is found to be immunogenic, it can be optimized by modifying its sequence to enhance its antigenicity, stability, and solubility. Only after confirming the results obtained at these two levels, researchers can focus on the finalized peptide in the clinical phases. The formulated peptide vaccine can then be tested in preclinical studies using animal models to evaluate its safety, efficacy, and immunogenicity. If the preclinical studies are promising, the peptide vaccine can be tested in clinical trials to evaluate its safety and efficacy in humans. Once the clinical trials are completed successfully, the peptide vaccine can be submitted for regulatory approval, which involves a thorough evaluation of its safety and efficacy over years of investigations [22,23].

3. Landscape of SARS-CoV-2 Peptide Vaccines on Clinical Trials

Based on the document published by the World Health Organization (WHO) [24], by February 2022, 146 vaccines are being developed to the clinical stage, and 159 vaccines are currently under investigation in the pre-clinical phase [25,26]. The subunit protein platform comprises 33% of all vaccines in the clinical phase (see Figure 2).

CoVepiT (OSE-13E) is a multivariate vaccine candidate versus SARS-CoV-2 in clinical stage 1. This peptides-based vaccine represents CD8+T-cell-mediated immune response against 11 different proteins of the SARS-CoV-2 virus including Spike, Membrane, Nucleocapsid, and several non-structural proteins. 48 non-COVID-19 volunteers received one single dose or two doses separated by 21 days and the safety and Immunogenicity of the vaccine were evaluated. CD8+ T cells responding to wild-type SARS-CoV-2 epitopes

remarkably increased after 22 days, 3, and 6 months of vaccination. the study was estimated in March 2022, but no other results have yet been published [27].

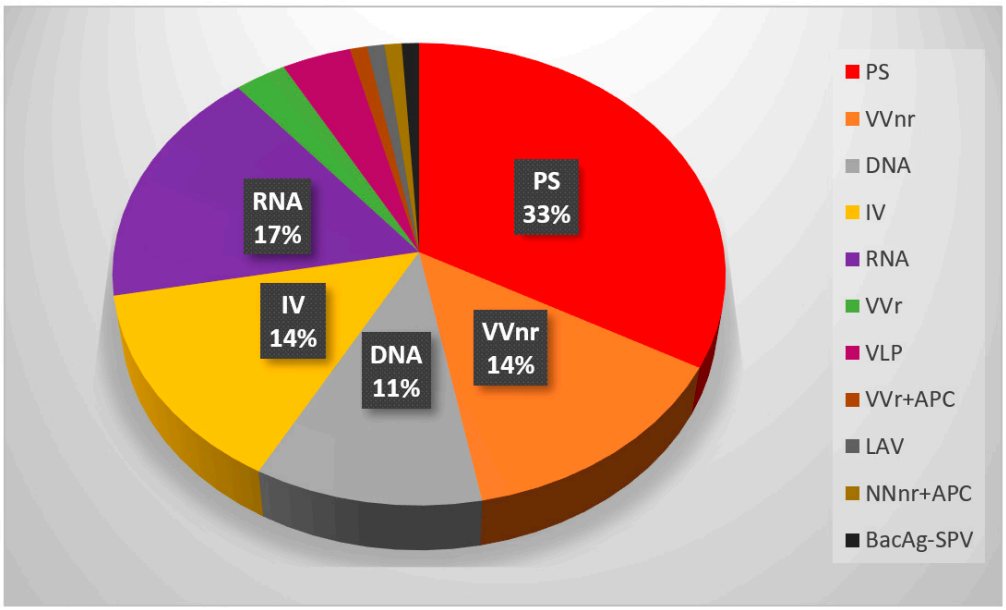

Figure 2. Candidates in the clinical phase, protein subunit vaccine includes the greatest percentage among vaccines in the clinical trial phase. The most candidate for the COVID-19 vaccine in the clinical trial phase is the Protein subunit (ps). After that, RNA, Viral Vector (non-replicating, Inactivated Virus (IV), and DNA vaccines have a higher portion of clinical trial phase vaccines. Protein subunit (ps), Viral Vector (non-replicating) (VVnr), Inactivated Virus (IV), Viral Vector (replicating) (VVr), Virus Like Particle (VLP), VVr + Antigen Presenting Cell (VVr + APC), Live Attenuated Virus (LAV), VVnr + Antigen Presenting Cell (NNnr + APC), Bacterial antigen-spore expression vector (BacAg-SPV).

Enrollments were selected among those who have received 2 doses of Vero cell (Inactivated COVID-19 vaccine). A dose of the recombinant COVID-19 vaccine will be administered in different time schedules (4–6 months, 7–9 months, and more than 9 months). In total, 3580 enrollment precipitated phases 1 and 2 in China. Following the results, phase 3 is going on 1848 enrollment in the United Arab Emirates. Furthermore, a study on Subject who has been vaccinated intramuscularly with three doses of the Recombinant COVID-19 vaccine (0, 30, and 60 days) is going [28]. The study is scheduled to be finished in February 2024.

COVAC-1 is a vaccine designed by the University of Saskatchewan against a specific portion of the spike protein of SARS-CoV-2 (S1 protein) spike protein. In addition, it contains three different TriAds adjuvants that can enhance the immune response. A multinational and Phase 1 trial on the Safety and immunogenicity is ongoing in different doses of S1 protein (25 and 50 µg) administered twice (4 weeks apart) in healthy adults. Although the promising safety and immunogenicity results of phase 1 of the vaccine were published in the journal Nature in November 2021 [18], they decided not to move forward with the study design (Withdrawn) [29].

Another phase 1 and phase 2 clinical trial study by the Beijing Institute of Microbiology and Epidemiology (Beijing, China) and Zhongyianke Biotech Co., Ltd. (Tianjin, China) was accomplished. 216 volunteers who received three doses of 40 µg SCoK (NCT04636333) showed appropriate safety and immunogenicity. SCoK is a recombinant SARS-CoV-2 vaccine (CHO cell). No severe local and systemic adverse effects in participating groups. The phase 3 clinical trial is under consideration on safety and antibody titer against the live virus [30].

The efficacy and safety of SCB-2019 (NCT04405908), a protein subunit vaccine, was evaluated in 216 healthy volunteers who received 2 doses of 3 µg to 30 µg vaccine. Also, the role of two different adjuvants in the immunogenicity of the vaccine, including CpG 1018 adjuvant plus Alum adjuvant and AS03 was investigated [31]. S-Trimer protein with both adjuvants demonstrated remarkable humoral and cellular immune responses against COVID-19. 30 microgram (µg) CpG 1018/Alum-adjuvanted SCB-2019 vaccine was selected as a suitable vaccine for phase 2 and 3 studies. The vaccine is administered as a booster dose after 4 months with a second injection. However, the study is active; results have not yet been published [32].

In a parallel study in Colombia, the safety of candidate SCB-2019 on 3820 <18 years old participants will accomplish. The study is a dose-finding and phase 2/3. The study is estimated to finish in July 2024 [33].

Another protein subunit vaccine is COVAX19 (Spikogen®) which Vaxine Pty Ltd. sponsors. The healthy volunteer received one dose of (25 µg) Spike antigen plus 15 mg Advax-CpG55.2™ adjuvant. The vaccine could make neutralizing antibodies against SARS-CoV-2. Following the appropriate finds of phases 1 and 2, Spikogen® was administered as a booster dose to assess the safety and titer of neutralizing antibodies [34]). No extreme adverse reaction was observed. The remarkable result is that the immune response was established against severe variants such as Omicron and Delta [35]. Another protein subunit vaccine is NVX-CoV2373, a recombinant spike protein of SARS-CoV-2. A Phase 1/2 and dose-finding study were assessed for safety and reactogenicity of alone NVX-CoV2373 vaccine and with Matrix-M1 adjuvant [36]. The finding showed all participants indicated high tolerated and immunogenicity with a 2-dose of 5 µg vaccine. Following the results, 1610 participants showed a gradual immune response, when administered as a booster dose of NVX-CoV2373 [37]. Figure 3 shows the schematic of the EpiVaCcorona vaccine, which is based on a peptide produced in Russia. In addition, some subunit protein vaccines that are undergoing clinical trial studies are described in Table 1.

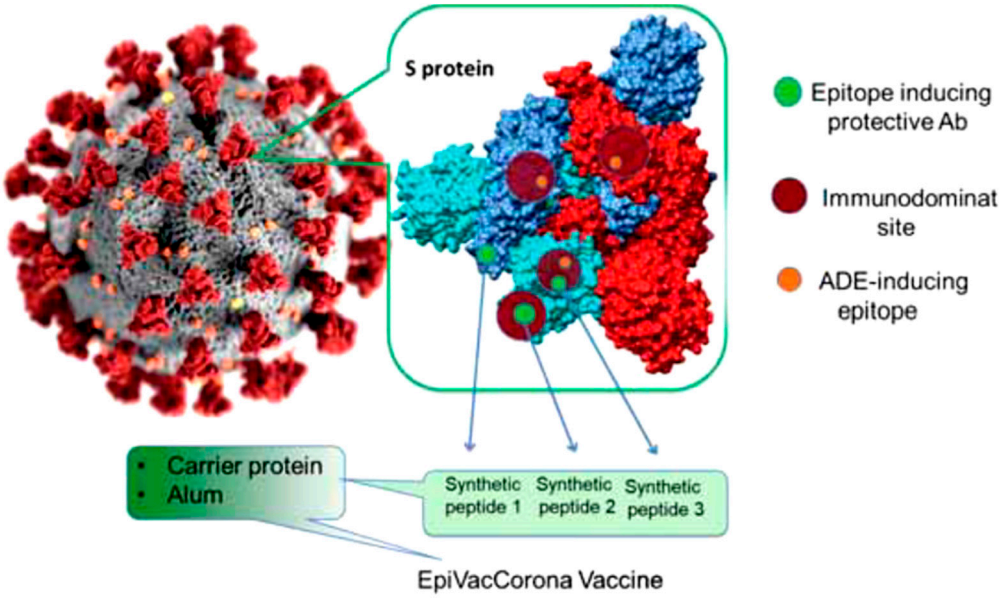

Figure 3. Schematic of EpiVacCorona (EpiVacCorona vaccine based on peptide antigens for the prevention of COVID-19). B cell epitopes (red circle) located on the virus s protein were selected using computer simulation methods. The immunogenic epitopes which lead to severe infection were excluded. From the 3 selected epitopes (green circle), peptides containing 20–31 amino acids were designed and synthesized. This platform contains three synthetic peptides similar to the s protein of SARS-2 conjugated to a chimeric recombinant protein carrier.

Table 1. Candidate protein subunit vaccines in clinical development.

Vaccine	Trial Registries	Developer	Enrollment	Phase
KBP-COVID-19 (RBD-based)	NCT04473690	Kentucky Bioprocessing Inc. (Owensboro, KY, USA)	101	Phase 1/2
VAT00008: SARS-CoV-2 S protein with adjuvant (1) CoV2 preS dTM monovalent D614 antigen, (2) Bivalent (2-antigen) vaccine comprising spike protein of D614 and spike protein of the SARS-CoV-2 Beta variant (B.1.351)	NCT04537208	Sanofi Pasteur (Lyon, France) + GSK (Brentford, UK)	442	Phase 3
CpG 1018/Alum-adjuvanted Recombinant SARS-CoV-2 Trimeric S-protein Subunit Vaccine (SCB-2019)	NCT05193279	Clover Biopharmaceuticals Inc. (Chengdu, China)/Dynavax (Emeryville, CA, USA)	1000	Phase 3
COVAX-19® Recombinant spike protein + adjuvant SPIKOGEN	NCT05175625	Vaxine Pty Ltd. (Adelaide, Australia)/CinnaGen Co. (Tehran, Iran)	300	Phase 3
MF59 adjuvanted SARS-CoV-2 Sclamp vaccine	NCT04806529	CSL Ltd. (Melbourne, Australia) + Seqirus (Holly Springs, NC, USA) + University of Queensland	-	Phase 2/3
FINLAY-FR1 anti-SARS-CoV-2 Vaccine (RBD + adjuvant)	RPCEC00000366	Instituto Finlay de Vacunas (La Habana, Cuba)	450	Phase 2
FINLAY-FR-2 anti-SARS-CoV-2 Vaccine (RBD chemically conjugated to tetanus toxoid plus adjuvant)	RPCEC00000354	Instituto Finlay de Vacunas (La Habana, Cuba)	44,031	Phase 3
EpiVacCorona (EpiVacCorona vaccine based on peptide antigens for the prevention of COVID-19)	NCT04780035	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology "Vector"	3000	Phase 3
RBD (baculovirus production expressed in Sf9 cells) Recombinant SARS-CoV-2 vaccine (Sf9 Cell)	NCT04904471	West China Hospital + Sichuan University WestVac Biopharma Co., Ltd. (Chengdu, China)	40,000	Phase 3
UB-612 (Multitope peptide based S1-RBD-protein based vaccine)	NCT04683224	Vaxxinity (Dallas, TX, USA)	60	Phase2/3
CIGB-66 (RBD+Aluminium hydroxide)	RPCEC00000359	Center for Genetic Engineering and Biotechnology (CIGB) Cuba	21,146	Phase 3
Recombinant SARS-CoV-2 Spike protein, Aluminum adjuvanted (Nanocovax)	NCT04922788	Nanogen Pharmaceutical Biotechnology, Ho Chi Minh City, Vietnam	13,000	Phase 3
Protein Subunit Recombinant Vaccine (Adjuvanted With Alum+CpG 1018)	NCT05525208	PT Bio Farma, Kota Bandung, Indonesia	900	Phase 2
Protein Subunit Recombinant Vaccine	NCT05546502	PT Bio Farma, Kota Bandung, Indonesia	1050 (Healthy Children)	Phase 3
RBD-based protein subunit vaccine (ZF2001)	NCT04833101	Jiangsu Province Centers for Disease Control and Prevention, Nanjing, China	120	Phase 4
Subunit recombinant vaccine	NCT05726084	St. Petersburg Research Institute of Vaccines and Sera, St. Petersburg, Russia	16,304	Phase 3
CpG 1018/Alum-adjuvanted SCB-2019 vaccine	NCT04672395	Clover BiopharmLtd., Altona North, Australia	31,454	Phase 3

Table 1. *Cont.*

Vaccine	Trial Registries	Developer	Enrollment	Phase
PIKA COVID-19 vaccine	NCT05463419	Yisheng Biopharma (Singapore) Pte. Ltd.	9300	Phase 3
ZR-202-CoV	NCT05313022	Shanghai Zerun Biotechnology Co.,Ltd., Shanghai, China	84	Phase 2
Booster dose of VidPrevtyn® Beta, Sanofi	NCT05749926	Assistance Publique-Hôpitaux de Paris, Paris, France	236	Phase 3

4. Monoclonal Antibodies (Mabs) as Potential Candidates for SARS-CoV-2 Treatment

Monoclonal antibodies work by binding to the spike protein of the SARS-CoV-2 virus, preventing it from entering human cells and replicating [38]. This can help reduce the severity of COVID-19 symptoms and shorten the duration of illness, particularly when administered early in the course of the disease. Several studies showed that cytokines including TNFα, IFN-ɣ, IL-2, IL-6, IL-7, IL-10, IL-17, IL-23, G-CSF, VEGF, GM-CSF, have vital roles in the progression and intensity of COVID-19. Thus, the administration of anti-cytokines and monoclonal antibodies could be a potentially effective treatment [39,40].

Infliximab is a TNFα inhibitor currently FDA-approved for treating autoimmune disorders, including Crohn's disease and rheumatoid arthritis. The study will enroll 18 hospitalized participants, in which the treatment group will receive 5 mg/kg intravenously between April and December 2020. Followed by the results published in Jun 2021 in the article. Infliximab can be used for clinical improvement in severe COVID-19 [41]. In another study, 18 hospitalized adults received a dose of 5 mg/kg Infliximab-abda by intravenous infusion. As the results showed, Infliximab could improve clinical recovery, due to reducing inflammatory storms.

Imatinib is a tyrosine kinase inhibitor that has been approved for the treatment of many hematologic and solid neoplasms. The in vitro activity of Imatinib against SARS-CoV was determined with EC50s (range, 9.8 to 17.6 μM). A Randomized Double-Blind and Phase 3 clinical study on the Safety and Efficacy of Imatinib for Hospitalized Adults with COVID-19 is ongoing in 204 participants. All patients receive 400 mg orally Imatinib daily for 14 days. Various outcome measures, including duration of hospitalization, mortality, and duration of invasive mechanical ventilation evaluate. Until February 2023, no results have yet been posted [42]. Imatinib's effectiveness was examined in a randomized, placebo-controlled clinical trial research conducted in the Netherlands with patients who had severe COVID-19 symptoms. The clinical trial planned to enroll 204 participants, in which the treatment group received a loading dose of 800 mg daily followed by 400 mg daily for 9 days. However, imatinib did not reduce the time to discontinuation of ventilation and supplemental oxygen, which demonstrated no beneficial effect on clinical symptoms [43].

F-652 is a recombinant IL-22-Fc fusion protein manufactured by Evive Biotech. A phase 2, multicenter and dose rising study is used in adult patients with COVID-19 pneumonia [44] (NCT05205668). In total, 60 patients enrolled in 2 cohorts of the study. In Cohort 1, the subjects will receive up to two intravenously of F-652 at dose 1 and subjects in Cohort 2 will receive up to two intravenously at dose 2 of F-652. The study completion date is estimated at March 2023, but no Safety, Pharmacokinetics, Pharmacodynamics, and Preliminary Efficacy result of F-652 have been posted [44,45].

Tocilizumab is an interleukin-6 (IL-6) inhibitor that is used for inflammatory diseases. In a Multicenter and Phase 3 clinical trial study by Hoffmann-La Roche, the efficacy of tocilizumab on 452 hospitalized patients was investigated (NCT04320615). Patients received a single dose of tocilizumab intravenously (8 mg/Kg). Interesting results showed that the mortality rate of patients receiving tocilizumab was not significantly different from the control group. Furthermore, tocilizumab could not reduce the virus load [46]. However, WHO has suggested tocilizumab for patients with severe infection. As described in Table 2, there are many Mabs in clinical trials for COVID-19 treatment.

Table 2. Monoclonal antibodies undergoing clinical trial phases.

Monoclonal Antibody	Trial Registries	Clinical Phase	Sponsor	Enrollment
Anti CD14 (CaTT)	NCT04391309	Phase 2	National Institute of Allergy and Infectious Diseases (NIAID)	40 hospitalized patients
LY3819253 (LY-CoV555) and LY3832479 (LY-CoV016)	NCT04427501	Phase 3	Eli Lilly and Company (Indianapolis, IN, USA)	3360 Mild to Moderate patients
CONDIVIDIAMO (Only Bamlanivimab Combination with Etesevimab	NCT05268601	-----	University of Milano Bicocca, Italy	1000 patients with Severe form
Casirivimab + Imdevimab REGN10933 + REGN10987	NCT04425629	Phase 3	Regeneron Pharmaceuticals (Rensselaer, NY, USA)	10078 mild and Ambulatory patients
Canakinumab	NCT04362813	Phase 3	Novartis Pharmaceuticals (Basel, Switzerland)	454 patients
BRII-196 and BRII-198	NCT04770467	Phase 2	Brii Biosciences, Inc. (Beijing, China)	17,495 mild and moderate patients
VIR-7831/GSK418236	NCT04545060	Phase 3	Vir Biotechnology, Inc. (San Francisco, CA, USA)	1057 Non-hospitalized Patients
Cizanlizumab	NCT04435184	Phase 2	Johns Hopkins University Novartis, USA	45 patients with vasculopathy
JS016	NCT04780321	Phase 2	Shanghai Junshi Bioscience Co., Ltd. (Shanghai, China)	62 patients with mild and moderate COVID-19
BGB-DXP593	NCT04551898	Phase 2	BeiGene (Cambridge, UK)	181 mild to moderate Patients
STI-1499 (COVI-GUARD)	NCT04454398	Phase 1	Sorrento Therapeutics, Inc. (San Diego, CA, USA)	-----
MAD0004J08	NCT04932850	Phase 1	Toscana Life Sciences Sviluppo s.r.l.	30 Healthy Adults
MANTICO Bamlanivimb + Etesevimab	NCT05205759	Phase 3	Azienda Ospedaliera Universitaria Integrata Verona	319 Mild or Moderate Patients
BRII-196 and BRII-198	NCT04787211	Phase 2	Brii Biosciences Limited (Beijing, China)	48 mild to moderate Patients
MAD0004J08	NCT04952805	Phase 2, Phase 3	Toscana Life Sciences Sviluppo s.r.l.	800 moderate's patients
Bamlanivimab or Casirivimab + Imdevimab	NCT04840459	Phase 2	Sohail Rao	1000 Non-Hospitalized Patients
SCTA01	NCT04644185	Phase 3	Sinocelltech Ltd. (Beijing, China)	795 Hospitalized Patients
DZIF-10c	NCT04631666	Phase 2	University of Cologne	57 mild to moderate Patients
CSL312 Garadacimab	NCT04409509	Phase 2	CSL Behring (King of Prussia, PA, USA)	124 patients
Inhalation DZIF-10c	NCT04631705	Phase 2	University of Cologne	45 healthy volunteers
AZD7442 (Tixagevimab [AZD8895] + Cilgavimab [AZD1061])	NCT04625725	Phase 3	AstraZeneca (Gaithersburg, MD, USA)	5254 healthy adults
Ravulizumab + Baricitinib	NCT04390464	Phase 4	Cambridge University Hospitals NHS Foundation Trust	1167 Hospitalized Patients

5. Conclusions and Future Perspective

Due to the advances in technology and science in the field of medicine, the future of vaccines is very broad and dynamic. Some of the developments that may be seen in the future for vaccines include combination vaccines that use several antigens to boost the body's immunity. Also, the use of carriers according to new technologies such as nanoparticles, liposomes, microcapsules, etc., increases the possibility of attacking the

virus and strengthening the body's immunity. The idea of long-lasting vaccines is also expected to gain momentum in the future. Some vaccines have created a challenge in the distribution and production of vaccines due to the need to re-inject them in short intervals. As technology advances, long-acting vaccines with lower doses and longer intervals between injections may be developed. But specifically in the case of SARS-CoV-2, in general, it seems that the solutions and strategies to deal with the new coronavirus are included in several social and economic areas, but from another point of view, this set of activities can be divided into pre- and post-pandemic states. According to the recent clinical results about monoclonal antibodies used against SARS-CoV-2, it is expected that in the near future, the candidates who have entered the phase 4 will be able to find permission to enter the marketing. Although more efforts should be made for the delivery of these medicinal applicants, the successful harvesting of the antibody-drug conjugate can also be used in this case, in such a way that the chemical drugs affecting the structure of the virus are connected to the structure of monoclonal antibodies using linkers to produce a vaccine that, in addition to suppressing the binding of the virus to the cell receptor, can also attack its structure.

Vaccination is considered one of the pre-and post-pandemic states. By vaccinating people after the outbreak of the disease, the spread of the virus can be controlled, and on the other hand, by vaccinating before the spread of the epidemic, it is possible to help fewer people become infected and the occurrence of the disease with milder symptoms in vaccinated people. The process of finalizing the peptide vaccine begins with the investigation of the proteome and the extraction of the viral protein complex. About the challenges of this path, information was reviewed that it is expected that a more accurate estimate of the final peptide sequence will be achieved in the future with further expansion of peptide isolation techniques and also the accuracy of determining the sequence of peptides that have an intracellular origin. Fortunately, in the case of the SARS-CoV-2, the approval process of produced vaccines took less than two years instead of the usual 15 years due to necessity (although it is still not clear that the future of this vaccination will be accompanied by complications). Considering the innovations that the scientific community was forced to implement in this short period, it may be possible to use other vaccines as well. In the case of peptide vaccines, the interaction between antigen and antibody is ultimately important, fortunately, the folding of the peptide is not very important, but the accuracy of its sequence and the absence of chemical changes are crucial. As a result, all considerations for the stabilization of medicinal proteins and therapeutic peptides should be considered for the storage and transfer of peptide vaccines to reduce the possibility of chemical changes in the peptides. Unfortunately, we are still dependent on glass containers for the storage of these types of drugs, which needs to be innovated to provide means for more reliable storage.

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References

1. Burrell, C.J.; Howard, C.R.; Murphy, F.A. Epidemiology of viral infections. *Fenner White's Med. Virol.* **2017**, 185–203. [CrossRef]
2. Zarkesh, K.; Entezar-Almahdi, E.; Ghasemiyeh, P.; Akbarian, M.; Bahmani, M.; Roudaki, S.; Fazlinejad, R.; Mohammadi-Samani, S.; Firouzabadi, N.; Hosseini, M.; et al. Drug-based therapeutic strategies for COVID-19-infected patients and their challenges. *Future Microbiol.* **2021**, *16*, 1415–1451. [CrossRef] [PubMed]
3. Fehr, A.R.; Perlman, S. Coronaviruses: An overview of their replication and pathogenesis. *Coronaviruses Methods Protoc.* **2015**, 1–23. [CrossRef]
4. Zhang, S.F.; Tuo, J.L.; Huang, X.B.; Zhu, X.; Zhang, D.M.; Zhou, K.; Yuan, L.; Luo, H.J.; Zheng, B.J.; Yuen, K.Y.; et al. Epidemiology characteristics of human coronaviruses in patients with respiratory infection symptoms and phylogenetic analysis of HCoV-OC43 during 2010–2015 in Guangzhou. *PLoS ONE* **2018**, *13*, e0191789. [CrossRef] [PubMed]
5. Fung, T.S.; Liu, D.X. Human coronavirus: Host-pathogen interaction. *Annu. Rev. Microbiol.* **2019**, *73*, 529–557. [CrossRef]
6. Peiris, M.; Poon, L.L.M. Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) (*Coronaviridae*). *Encycl. Virol.* **2021**, 814–824. [CrossRef]
7. World Health Organization. Coronavirus 2020. Available online: https://www.who.int/emergencies/diseases/novel-coronavirus-2019 (accessed on 4 July 2020).
8. Zhu, N.; Zhang, D.; Wang, W.; Li, X.; Yang, B.; Song, J.; Zhao, X.; Huang, B.; Shi, W.; Lu, R.; et al. A novel coronavirus from patients with pneumonia in China, 2019. *N. Engl. J. Med.* **2020**, *382*, 727–733. [CrossRef]
9. Matricardi, P.M.; Dal Negro, R.W.; Nisini, R. The first, holistic immunological model of COVID-19: Implications for prevention, diagnosis, and public health measures. *Pediatr. Allergy Immunol.* **2020**, *31*, 454–470. [CrossRef]
10. Shang, J.; Ye, G.; Shi, K.; Wan, Y.; Luo, C.; Aihara, H.; Li, F. Structural basis of receptor recognition by SARS-CoV-2. *Nature* **2020**, *581*, 221–224. [CrossRef]
11. Dong, M.; Zhang, J.; Ma, X.; Tan, J.; Chen, L.; Liu, S.; Xin, Y.; Zhuang, L. ACE2, TMPRSS2 distribution and extrapulmonary organ injury in patients with COVID-19. *Biomed. Pharmacother.* **2020**, *131*, 110678. [CrossRef]
12. Akbarian, M.; Lundstrom, K.; Redwan, E.M.; Uversky, V.N. Vaccine Development Strategies and the Current Status of COVID-19 Vaccines. In *COVID-19: From Bench to Bedside*; CRC Press: Boca Raton, FL, USA, 2022.
13. Lucchese, G. Epitopes for a 2019-nCoV vaccine. *Cell. Mol. Immunol.* **2020**, *17*, 539–540. [CrossRef] [PubMed]
14. Song, Z.; Xu, Y.; Bao, L.; Zhang, L.; Yu, P.; Qu, Y.; Zhu, H.; Zhao, W.; Han, Y.; Qin, C. From SARS to MERS, thrusting coronaviruses into the spotlight. *Viruses* **2019**, *11*, 59. [CrossRef]
15. Purcell, A.W.; McCluskey, J.; Rossjohn, J. More than one reason to rethink the use of peptides in vaccine design. *Nat. Rev. Drug Discov.* **2007**, *6*, 404–414. [CrossRef] [PubMed]
16. Nelde, A.; Rammensee, H.G.; Walz, J.S. The peptide vaccine of the future. *Mol. Cell. Proteom.* **2021**, *20*, 100022. [CrossRef] [PubMed]
17. Kianpour, M.; Akbarian, M.; Uversky, V.N. Nanoparticles for coronavirus control. *Nanomaterials* **2022**, *12*, 1602. [CrossRef] [PubMed]
18. Heitmann, J.S.; Bilich, T.; Tandler, C.; Nelde, A.; Maringer, Y.; Marconato, M.; Reusch, J.; Jäger, S.; Denk, M.; Richter, M.; et al. A COVID-19 peptide vaccine for the induction of SARS-CoV-2 T cell immunity. *Nature* **2022**, *601*, 617–622. [CrossRef]
19. Bartlam, M.; Xu, Y.; Rao, Z. Structural proteomics of the SARS coronavirus: A model response to emerging infectious diseases. *J. Struct. Funct. Genom.* **2007**, *8*, 85–97. [CrossRef]
20. Stukalov, A.; Girault, V.; Grass, V.; Bergant, V.; Karayel, O.; Urban, C.; Haas, D.A.; Huang, Y.; Oubraham, L.; Wang, A.; et al. Multi-level proteomics reveals host-perturbation strategies of SARS-CoV-2 and SARS-CoV. *bioRxiv* **2020**, *1*, 1.
21. Dudek, N.L.; Croft, N.P.; Schittenhelm, R.B.; Ramarathinam, S.H.; Purcell, A.W. A systems approach to understand antigen presentation and the immune response. *Proteom. Syst. Biol. Methods Protoc.* **2016**, *1394*, 189–209.
22. Faridi, P.; Purcell, A.W.; Croft, N.P. In immunopeptidomics we need a sniper instead of a shotgun. *Proteomics.* **2018**, *18*, 1700464. [CrossRef]
23. Ihling, C.; Tanzler, D.; Hagemann, S.; Kehlen, A.; Huttelmaier, S.; Arlt, C.; Sinz, A. Mass spectrometric identification of SARS-CoV-2 proteins from gargle solution samples of COVID-19 patients. *J. Proteome Res.* **2020**, *19*, 4389–4392. [CrossRef] [PubMed]
24. Worl Health Organization. Draft Landscape of COVID-19 Candidate Vaccines. 2 July 2020. Available online: https://www.who.int/publications/m/item/draft-landscape-of-COVID-19-candidate-vaccines (accessed on 4 July 2020).
25. Fares, S.; Elmnyer, M.M.; Mohamed, S.S.; Elsayed, R. COVID-19 vaccination perception and attitude among healthcare workers in Egypt. *J. Prim. Care Community Health* **2021**, *12*, 21501327211013303. [CrossRef] [PubMed]
26. Yan, Z.P.; Yang, M.; Lai, C.L. COVID-19 vaccines: A review of the safety and efficacy of current clinical trials. *Pharmaceuticals* **2021**, *14*, 406. [CrossRef] [PubMed]
27. OSE Immunotherapeutics. A Randomized, Open Label, Phase 1 Study to Evaluate the Safety, Reactogenicity and Immunogenicity of OSE-13E, a Multiepitope-Based Vaccine Candidate against COVID-19, in Healthy Adults (COVEPIT-3). Clinical Trial Registration NCT04885361. 2021. Available online: https://clinicaltrials.gov/ct2/show/NCT04885361 (accessed on 26 June 2023).
28. Belayachi, J.; Obtel, M.; Mhayi, A.; Razine, R.; Abouqal, R. Long term effectiveness of inactivated vaccine BBIBP-CorV (Vero Cells) against COVID-19 associated severe and critical hospitalization in Morocco. *PLoS ONE* **2022**, *17*, e0278546. [CrossRef]

29. Garnett, L.; Tran, K.; Chan, M.; Tierney, K.; Schiffman, Z.; Audet, J.; Lew, J.; Meilleur, C.; Chan, M.; Manguiat, K.; et al. An S1 subunit vaccine and combination adjuvant (COVAC-1) elicits robust protection against SARS-CoV-2 challenge in African green monkeys. *bioRxiv* **2022**, 6. [CrossRef]
30. Luo, D.; Pan, H.; He, P.; Yang, X.; Li, T.; Ning, N.; Fang, X.; Yu, W.; Wei, M.; Gao, H. A randomized, double-blind, placebo-controlled phase 1 and phase 2 clinical trial to evaluate efficacy and safety of a SARS-CoV-2 vaccine SCoK in adults. *Clin. Transl. Med.* **2022**, *12*, e1016. [CrossRef] [PubMed]
31. Richmond, P.; Hatchuel, L.; Dong, M.; Ma, B.; Hu, B.; Smolenov, I.; Li, P.; Liang, P.; Han, H.H.; Liang, J.; et al. Safety and immunogenicity of S-Trimer (SCB-2019), a protein subunit vaccine candidate for COVID-19 in healthy adults: A phase 1, randomised, double-blind, placebo-controlled trial. *Lancet* **2021**, *397*, 682–694. [CrossRef] [PubMed]
32. A Controlled Phase 2/3 Study of Adjuvanted Recombinant SARS-CoV-2 Trimeric S-protein Vaccine (SCB-2019) for the Prevention of COVID-19. NCT04672395. Available online: www.ClinicalTrials.gov (accessed on 26 June 2023).
33. Lopez, P.; Bravo, L.; Buntinx, E.; Borja-Tabora, C.; Velasquez, H.; Rodriguez, E.J.; Rodriguez, C.A.; Carlos, J.; Montellano, M.E.; Alberto, E.R. Safety and immunogenicity of SCB-2019, an adjuvanted, recombinant SARS-CoV-2 trimeric S-protein subunit COVID-19 vaccine in healthy 12–17 year-old adolescents. *medRxiv* **2023**, *2*, 23286317. [CrossRef]
34. Tabarsi, P.; Anjidani, N.; Shahpari, R.; Roshanzamir, K.; Fallah, N.; Andre, G.; Petrovsky, N.; Barati, S. Immunogenicity and safety of SpikoGen®, an adjuvanted recombinant SARS-CoV-2 spike protein vaccine as a homologous and heterologous booster vaccination: A randomized placebo-controlled trial. *Immunology* **2022**, *167*, 340–353. [CrossRef]
35. Tabarsi, P.; Anjidani, N.; Shahpari, R.; Mardani, M.; Sabzvari, A.; Yazdani, B.; Kafi, H.; Fallah, N.; Ebrahimi, A.; Taheri, A.; et al. Evaluating the efficacy and safety of SpikoGen®, an Advax-CpG55. 2–adjuvanted severe acute respiratory syndrome coronavirus 2 spike protein vaccine: A phase 3 randomized placebo-controlled trial. *Clin. Microbiol. Infect.* **2023**, *29*, 215–220. [CrossRef]
36. Mallory, R.M.; Formica, N.; Pfeiffer, S.; Wilkinson, B.; Marcheschi, A.; Albert, G.; McFall, H.; Robinson, M.; Plested, J.S.; Zhu, M.; et al. Safety and immunogenicity following a homologous booster dose of a SARS-CoV-2 recombinant spike protein vaccine (NVX-CoV2373): A secondary analysis of a randomised, placebo-controlled, phase 2 trial. *Lancet Infect. Dis.* **2022**, *22*, 1565–1576. [CrossRef] [PubMed]
37. Medicine UNLo. Evaluation of the Safety and Immunogenicity of a SARS-CoV-2 rS (COVID-19) Nanoparticle Vaccine with/without Matrix-M. Adjuvant. Available online: https://clinicaltrials.gov/ct2/show/NCT04368988 (accessed on 26 June 2023).
38. Chavda, V.P.; Bezbaruah, R.; Dolia, S.; Shah, N.; Verma, S.; Savale, S.; Ray, S. Convalescent plasma (hyperimmune immunoglobulin) for COVID-19 management: An update. *Process Biochem.* **2023**, *127*, 66–81. [CrossRef] [PubMed]
39. Ragab, D.; Salah Eldin, H.; Taeimah, M.; Khattab, R.; Salem, R. The COVID-19 cytokine storm; what we know so far. *Front. Immunol.* **2020**, *11*, 1446. [CrossRef]
40. Pan, C.; Chen, H.; Xie, J.; Huang, Y.; Yang, Y.; Du, B.; Qiu, H. The Efficiency of Convalescent Plasma Therapy in the Management of Critically Ill Patients Infected With COVID-19: A Matched Cohort Study. *Front. Med.* **2022**, *9*, 822821. [CrossRef]
41. Hachem, H.; Godara, A.; Schroeder, C.; Fein, D.; Mann, H.; Lawlor, C.; Marshall, J.; Klein, A.; Poutsiaka, D.; Breeze, J.L.; et al. Rapid and sustained decline in CXCL-10 (IP-10) annotates clinical outcomes following TNFα-antagonist therapy in hospitalized patients with severe and critical COVID-19 respiratory failure. *J. Clin. Transl. Sci.* **2021**, *5*, e146. [CrossRef] [PubMed]
42. Emadi, A.; Chua, J.V.; Talwani, R.; Bentzen, S.M.; Baddley, J. Safety and Efficacy of Imatinib for Hospitalized Adults with COVID-19, A structured summary of a study protocol for a randomised controlled trial. *Trials* **2020**, *21*, 897. [CrossRef]
43. Atmowihardjo, L.; Schippers, J.R.; Bartelink, I.H.; Bet, P.M.; van Rein, N.; Purdy, K.; Cavalla, D.; Comberiati, V.; McElroy, A.; Snape, S.D.; et al. The invent COVID trial: A structured protocol for a randomized controlled trial investigating the efficacy and safety of intravenous imatinib mesylate (Impentri®) in subjects with acute respiratory distress syndrome induced by COVID-19. *Trials* **2022**, *23*, 158. [CrossRef] [PubMed]
44. Arab, J.P.; Sehrawat, T.S.; Simonetto, D.A.; Verma, V.K.; Feng, D.; Tang, T.; Dreyer, K.; Yan, X.; Daley, W.L.; Sanyal, A.; et al. An open-label, dose-escalation study to assess the safety and efficacy of il-22 agonist f-652 in patients with alcohol-associated hepatitis. *Hepatology* **2020**, *72*, 441–453. [CrossRef]
45. Tang, K.-Y.; Lickliter, J.; Huang, Z.-H.; Xian, Z.-S.; Chen, H.-Y.; Huang, C.; Xiao, C.; Wang, Y.-P.; Tan, Y.; Xu, L.-F.; et al. Safety, pharmacokinetics, and biomarkers of F-652, a recombinant human interleukin-22 dimer, in healthy subjects. *Cell. Mol. Immunol.* **2018**, *16*, 473–482. [CrossRef]
46. Rosas, I.O.; Bräu, N.; Waters, M.; Go, R.C.; Malhotra, A.; Hunter, B.D.; Bhagani, S.; Skiest, D.; Savic, S.; Douglas, I.S.; et al. Tocilizumab in patients hospitalised with COVID-19 pneumonia: Efficacy, safety, viral clearance, and antibody response from a randomised controlled trial (COVACTA). *Eclinicalmedicine* **2022**, *47*, 101409. [CrossRef]