CPQ Microbiology (2022)
Short Communication

Third-Stage COVID-19 Disease Still Needs Remedy

Shimon Shatzmiller

Department of Biological Chemistry, Ariel University, Ariel 40700, Israel

***Correspondence to:** Dr. Shimon Shatzmiller, Department of Biological Chemistry, Ariel University, Ariel 40700, Israel.

Copyright

Received: 21 July 2022

Published: 28 July 2022

Keywords: *COVID-19; SARS-CoV-2*

The novel coronavirus disease 2019 (COVID-19) progresses in four stages [1]. The first stage is a presymptomatic phase, which may lead to stage 2, which presents with fever, cough, generalized malaise, and a high viral load. This is followed, after seven to ten days, by stage 3, which presents with viral pneumonia. Most patients improve clinically as immunological responses are developed at this stage. However, during stage 3, a small number of patients develop symptoms of hypercytokinemia ("cytokine storm"). Finally, in stage 4, acute respiratory distress syndrome (ARDS) and multiorgan failure sets in, with a high reported mortality rate [1]. The respiratory symptoms caused by COVID-19 thus stem from inflammation that causes lung injury. This causes a decrease in oxygen saturation. If the inflammation, marked by the "cytokine storm," is not mitigated, it can lead to ARDS [1]; therefore, the aim of therapy should be to abort the "cytokine storm" [2].

COVID 19 and Organ Damage

Several pro-inflammatory cytokines can induce cell death in various cell types, leading to pathological conditions. In a study conducted on 416 patients affected with COVID-19, cardiac injury was present in about 19.7% during hospitalization of the patients [3]. There is a possibility that COVID-19 causes myocardial cell injury either directly by interacting with the angiotensin-converting enzyme-2 (ACE2) receptors or indirectly by other mechanisms [4]. In the case of ACE2 receptors, it is hypothesized that the COVID-19 first attacks several organs expressing ACE2 receptors, such as the heart, brain, vessels, liver, kidney, and, more importantly, lung [5]. Several lines of evidence declare that COVID-19 may cause brain injury via direct and indirect mechanisms.

Staats *et al.* [2] reported on two patients who showed marked improvement of clinical symptoms after application of transcutaneous cervical vagus nerve stimulation (VNS), but the authors did not report on objective measurements of at least one of the proinflammatory cytokines. In addition, clinical evidence has been reported: auricular electroacupuncture, another form of auricular VNS, may inhibit the production of tumor necrosis factor (TNF) alpha, interleukin (IL) -1 beta, IL-6 and IL-8, among others. [6]. They argued that it was advantageous for treating the inflammatory processes associated with COVID-19. Finally, there is evidence that IL-6 plasma levels are prognostic indicators of COVID-19 progression [7,8].

We report on two patients with stage 3 COVID-19 in whom IL-6 levels were markedly elevated and transcutaneous auricular VNS (taVNS) may have drastically reduced IL-6 blood levels over a relatively short period of time. taVNS stimulation was selected on the strength of the Staats *et al.* [2] and Jin *et al.* [3] reports. Both patients gave consent to publish these case reports. The institution where the work was done does not require Institutional Review Board approval for single case reports [9].

Infection with SARS-CoV-2 (or COVID-19) can be classified into three stages of increasing severity:

a. Stage I: The starting of the infection or viral response phase during which symptoms of upper respiratory tract infection dominate.

b. Stage II: The pulmonary phase when the patients develop full-blown pneumonia with all its associated symptoms.

c. Stage III: The hyperinflammation phase when patients develop acute respiratory distress syndrome (ARDS), sepsis, and kidney and other organ failures.

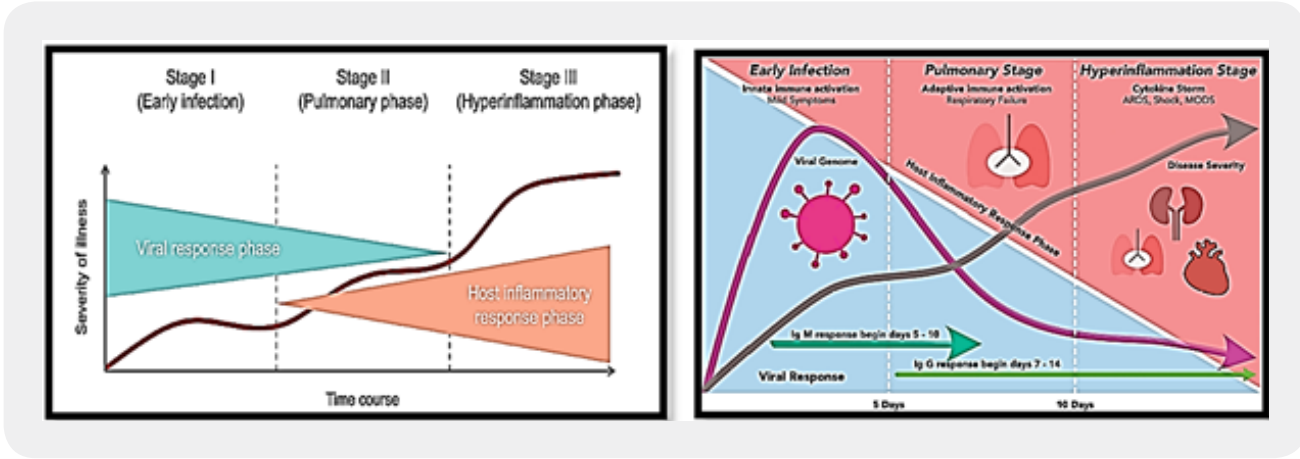


Figure: *MODS, a disorder of multi-organ dysfunction.(credit ref. [10])*

The steps of COVID-19. COVID-19 can be separated into 3 stadiums: the early, pulmonary and hyper-inflammatory stage. In early infection, the viral load (purple line in the blue area) begins to rise and at certain points it begins to activate the host's immune response (red area). As the disease progresses to a more severe

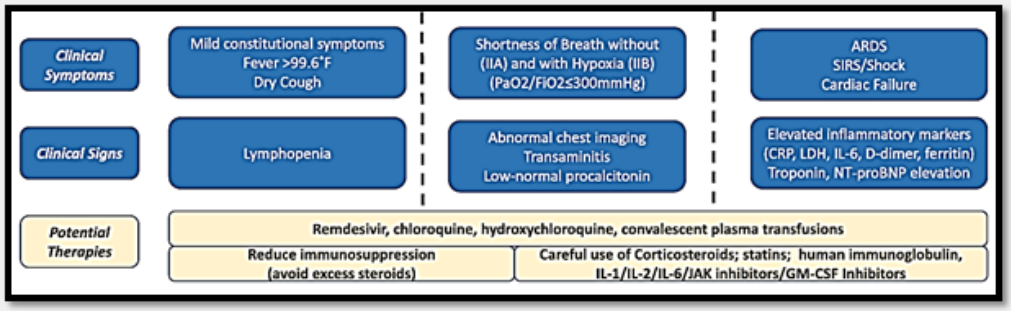
condition, the pro-inflammatory cytokines accumulate and begin to form antibodies against the virus. When the disease is not treated immediately, COVID-19 may fall into a combination of over-inflammation, organ failure and death. Abbreviations: ARDS, acute respiratory distress syndrome;

Similar to many antiviral medicines, Paxelvide works best in the early stages of the disease - in this case. In the first five days of symptoms, says Jeffrey Topal, MD, an infectious disease specialist at Yale Medicine. (He is involved in determining COVID-19 treatment protocols for Yale-New Haven Hospital Patients). The first day of the illness are when the virus is eradicated. After this time period, the disease changes. It becomes a struggle of the patients immune system with the rest of the virus but mainly to combat the factors created in the system due toi virus activity.

The pandemic has also triggered numerous global initiatives to tackle the newly emerging disease, including the development of SARS-CoV-2 vaccines and the attempt to discover potential pharmacological therapies. Nonetheless, despite the success of SARS-CoV-2 vaccine development, COVID-19 therapy remains challenging. Several repurposed drugs that were found useful in small clinical trials are ineffective in larger studies. Additionally, the pathophysiology of SARS-CoV-2 infection displayed the predominance of hyperinflammation and immune dysregulation in inducing multiorgan damage. Therefore, the potential benefits of both immune modulation and suppression in COVID-19 have been extensively discussed. Here, we describe the roles of immunomodulation as possible COVID-19 pharmacological modalities. Based on the existing data and proposed several new immunologic targets to be tested in the foreseeable future.

Most patients pass the first stage which may end the attack of the corona virus on their body. However, the rest may suffer from mant life threatening complication due toi the action of the innune system prortecting the body. Here, Classification of COVID-19 disease states and potential therapeutic targets. The figure illustrates 3 escalating phases of COVID-19 disease progression, with associated signs, symptoms, and potential phase-specific therapies., Acute respiratory distress syndrome (ARDS; CRP, a C-reactive protein; JAK, Janus Kinaz; LDH, lactate dehydrogenase; NT-proBNP, N-terminal pro B-type naturopathic peptide SIRS, systemic inflammatory response syndrome; GM-CSF, Granulocyte Macrophage.

Colony Stimulating Factor. JAK: Because the family members of the type I and type II cytokine receptors do not catalytic kinase activity, they rely on the JAK family of tyrosine kinases to phosphorylate and activate downstream proteins involved in their signal transduction pathways. The receptors exist as paired polypeptides, thus exhibiting two intracellular signal-transducing domains.



Classification of COVID-19 disease states and potential therapeutic targets. The figure illustrates 3 escalating phases of COVID-19 disease progression, with associated signs, symptoms, and potential phase-specific therapies. ARDS, acute respiratory distress syndrome; CRP, C-reactive protein; JAK, janus kinase; LDH, lactate dehydrogenase; NT-proBNP, N-terminal pro B-type natriuretic peptide; SIRS, systemic inflammatory response syndrome; GM-CSF, Granulocyte Macrophage Colony Stimulating Factor.

Future Immunologic Targets for COVID-19 [10]

In the future, a number of new immunological targets, such as Tumor Necrosis Factor-inhibitors (TNF) -α,

In the future, some new immunological targets, such as tumor necrosis factor inhibitors (TNF) -α, retinogenic I-like gene receptor (RLR) and mTOR inhibitors, NLRP3 inflammation inhibitors, complement inhibitors, toll-like receptor modulators, IL-18 inhibitors and possibly The secretion of mesenchymal stem cells may be tested due to their reported significance in the pathogenesis of COVID-19 [10].

Retinogenic I-like gene receptor (RLR) and mTOR inhibitors, NLRP3 inflammation inhibitors, complement inhibitors, toll-like receptor modulators, IL-18 inhibitors, and possibly The secretion of mesenchymal stem cells may be tested due to their reported significance in the pathogenesis of COVID-19.

Several clinical trials have investigated the potential role of complement inhibitors in COVID-19.68 For Country of C5 Eculizumab inhibitors and JAK Baricitinib inhibitors, currently entering Phase IV, [11] clinical trial. The third stage, hyper-inflammatory, occurs when an activated immune system can cause damage to the heart, kidneys and other organs, they said.

At this point, the study noted that a "storm cytokine" - in which the body attacks its tissues - may occur. Although there may be an overlap between the three stages of the disease, the scientists said it is important to recognize each stage in order to tailor customized treatment to patients. because, many, of, the drugs are, being, for, and, these, be, on, which, what, as. drugs used to treat people with COVID-19 are still being researched for safety and efficacy, the researchers said these experimental treatments should be evaluated based on the specific stage of the disease to which they are enrolled and what happens to the body as COVID-19 progresses. The scientists suggested a customized treatment plan with some medications and potential treatments in the review. According to them, in the early stages of infection, it was found that plasma containing antibodies from COVID-19 patients who recovered reduces the number of infectious virus particles in the body. According to the study authors, antiviral drugs, including remdesivir, which helped prevent viral replication in stage 1, may be beneficial in stage 2. According to them, activating tissue plasminogen (tPA) - a drug used to treat stroke - breaks down blood clots that can occur during stage 2 [7].

The researchers said that anti-inflammatory drugs like corticosteroids, tocilizumab and sarilumab may help reduce systemic inflammation in stages 2 and 3.

The scientists added that the heparin anticoagulant drug is important at every stage of the disease to prevent blood clots in blood vessels and capillaries.

However, they warned that there are no proven drugs to treat COVID-19.

"We are now entering a new era of the epidemic, with many randomized controlled trials aimed at identifying patient-specific drugs, and drugs that are more appropriate for the specific stage of the disease with improved accuracy," the scientists noted [12].

Meanwhile, RLR is activated following the detection of viral RNA in the cytoplasm of infected cells, which initiates production of type I and III IFNs and inflammatory cytokines [13], inhibition of RLR can alter the interactions between host and viral factors, which may be potential. Prevent the activation of excessive inflammatory response in COVID-19. Previous studies have also reported activation of NLRP3 in COVID-19 [14], which facilitates the initiation of major proinflammatory cytokines, such as IL-1β and IL-18. Therefore, inhibitors of an NLRP3 inflammasome and its downstream mediators (e.g., IL-1β and IL-18) may reduce COVID-19-associated morbidity and mortality by minimizing the hyper-inflammatory condition. Finally, although it is still early stage, the possible contributions of mesenchymal stem cells and their secretion under COVID-19 management are being investigated [15]. However, these potential targets remain at the investigation stage and further extensive trials and clinical trials. Studies are needed to evaluate their efficacy in COVID-19. As lethality is directly correlated with disease severity, hospitalized severe cases are of the greatest importance to reduce, especially the cytokine storm phenomenon. This severe inflammatory phenomenon characterized by elevated levels of inflammatory mediators can be targeted to relieve symptoms and save the infected patients. One of the promising therapeutic strategies to combat COVID-19 is nucleic acid-based therapeutic approaches, including microRNAs (miRNAs). This work is an up-to-date review aimed to comprehensively discuss the current nucleic acid-based therapeutics against COVID-19 and their mechanisms of action, considering the emerging SARS-CoV-2 variants of concern and providing potential future directions. miRNAs can be used to run interference with the expression of viral proteins, while endogenous miRNAs can be targeted as well, offering a versatile platform to control SARS-CoV-2 infection. By targeting these miRNAs, the COVID-19-induced cytokine storm can be suppressed. therefore, nucleic acid-based therapeutics (miRNAs included) have a latent ability to break the COVID-19 infection in general and quell the cytokine storm in particular.

The astonishing number of confirmed cases and deaths globally has spurred the rapid development of therapeutics and vaccine approaches. The urgent need for effective vaccines and antiviral therapeutics has made it urgent to explore promising unconventional technologies that have the advantage of rapid development towards the swift counteraction of the pandemic [16]. Therefore, in the early months of the COVID-19 pandemic, several research groups and institutions realized that the potential solution could lie within the nucleic acid-based approaches, which allow for the quick response needed to overcome this global pandemic. Thus, several nucleic acid-based therapeutics and vaccines have been proposed. Two of them (i.e., the Moderna and Pfizer–BioNTech vaccines) are among six vaccines that passed the clinical evaluations and received emergency authorization [17]. Although nucleic acid-based technology is a relatively new class for developing therapeutics and vaccines, it has surprised the scientific community and shown effective and promising outcomes. Therefore, the current revolution in nucleic acid-based technology to develop therapeutics and vaccines against COVID-19 deserves to be discussed in depth. This review summarizes the recent advances in developing nucleic acid-based therapeutics and vaccines against COVID-19 and

suggests a potential nucleic acid-based therapy for targeting cytokine storms in COVID-19 [18] patients. In addition, Inovio's Pan-COVID-19 vaccination can elicit cross-reactive immune responses against both existing and emerging virus strains [19].

Cytokine Storm

COVID-19 patients demonstrate elevated serum IgM, IgG, and IgA levels, with even higher levels in severe cases [130]. Inflammatory mediators such as IFN-γ, tumor necrosis factor (TNF), IL-2, IL-6, and IL-10 were also elevated in COVID-19 patients, and higher levels were reported in the severe cases [20]. In addition, IL-1β and IL-8 were reported with a high level in infected patients [21]. The increase in cytokines (hypercytokinemia) leads to a lethal inflammatory response referred to as a cytokine storm. In severe cases of about 15% of COVID-19 patients, life-threatening ARDS was found due to alveolar damage by the inflammatory mediators [22]. Targeting the inflammatory response-regulating pathways, such as the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway, might protect from ARDS development [23]. However, in critical cases, treatment or elimination of the cytokine storm might be complex, even with many involved therapeutic targets in the immunopathogenesis [24]. Therefore, early cytokine storm management has significant value in reducing mortality, especially in severe cases.

The elevated level of inflammatory mediators often correlated with the SARS-CoV-2 infection severity, including cytokines and chemokines such as IL-2, IL-6, IL-10, TNF, C-reactive protein, ferritin, and D-dimers [25]. The IL-6 blood level correlates with the SARS-CoV-2 infection mortality [26]. Therefore, the high levels of inflammatory mediators (cytokine storm) indicate that SARS-CoV-2 lethality, which is presented as cytokine release syndrome (CRS) [18,27], could be managed via IL-6 inhibition [28]. Figure 2 illustrates the previously discussed targets, and more, for combating the SARS-CoV-2 infection. The inflammatory mediators and other possible targets could be the aim of nucleic acid-based therapeutics to develop novel and perhaps effective therapeutics for controlling the COVID-19 infection risk.

https://www.mdpi.com/2075-4426/12/3/386/htm

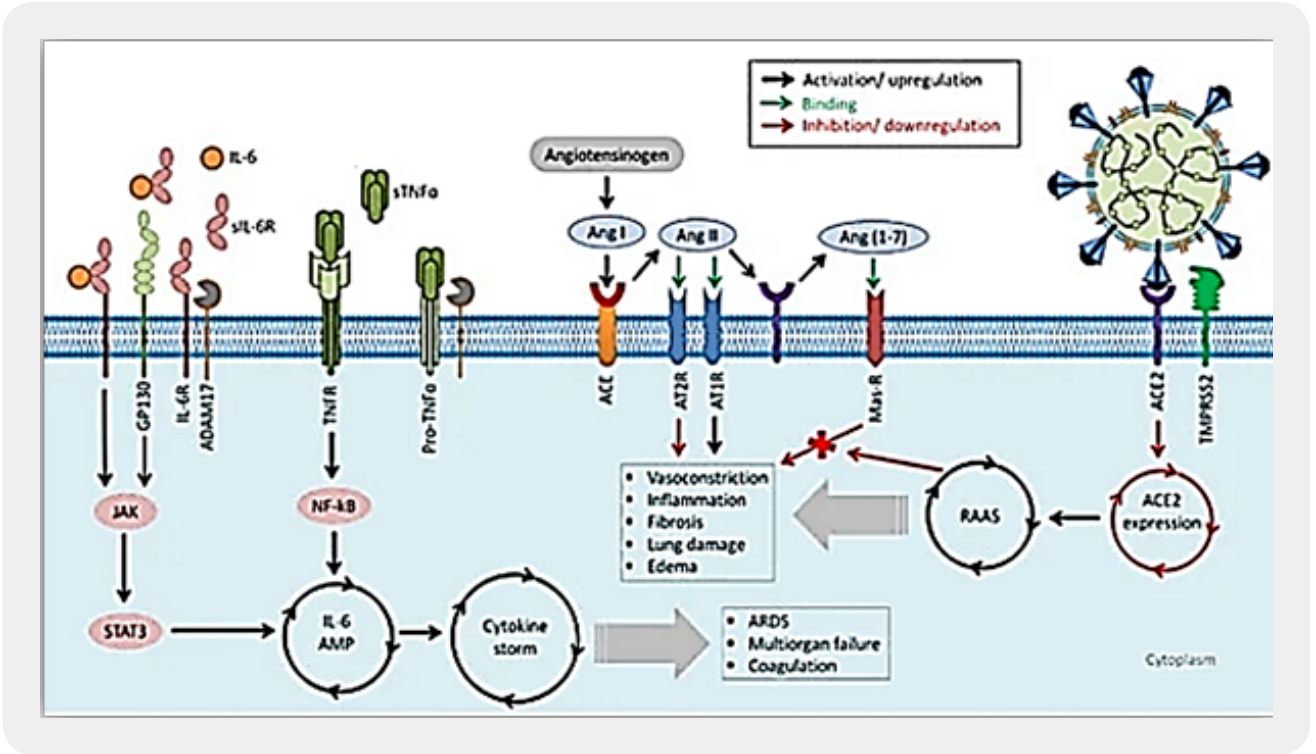


Figure 2: *Scheme of possible targets for developing therapeutics against COVID-19 and the presented cytokine release syndrome (CRS). SARS-CoV-2 utilizes ACE2 and TMPRSS2 as cell entry receptors. (credit ref [])*

Survival and Programmed Cell Death by Cytokines [29,30]. Cytokines are a broad and released category of small proteins (~ 20-20 kDa) that are important in cell signaling. Cytokines are peptides and cannot cross the lipid bilayer of cells to enter the cytoplasm. Cytokines are shown to be implicated in autocrine, paracrine, and endocrine signaling as anti-vaccine agents. Their distinct distinction from hormones is still part of ongoing research.

A cytokine storm is a human bodily reaction in which the innate immune system releases a large number of cytokines, potentially overwhelming the body and possibly leading to fatality.

Coronavirus Virus 2019 (COVID-19) Quickly spread throughout the whole region of earth. This is significantly related mortality, especially in at-risk groups with poor prognostic features in the hour Hospitalization. The spectrum of diseases. It is broad but in constant battle, hospitalized with COVID-19, Pneumonia, Sepsis, Breathing Failure, and Acute Respiratory distress Syndrome (ARDS) often Encountered complications [31,32].

Cytokine-release syndrome (CRS), which can be fatal if not properly identified and managed. Creative Biolabs offers the most extensive portfolio of CRS immunoassay platforms and services for measuring CRS-associated inflammatory cytokines and evaluating CRS process. Whether you need qualitative or quantitative results, have limited sample, require single or multianalyte analysis, you will be able to find

an optimal solution from Creative Biolabs. One-stop Cytokine Release Syndrome (CRS) Management Solutions [33].

COVID-19 Nucleic Acid-Based Therapeutics

Among the promising strategies to combat SARS-CoV-2 is nucleic acid-based therapeutics. Therapeutic nucleic acids (TNAs) include many pioneering technologies such as antisense oligonucleotides (ASOs), micro RNAs (miRNAs), small interfering RNAs (siRNAs), clustered regularly interspaced short palindromic repeats–CRISPR-associated protein (CRISPR–Cas), and mRNA vaccines [34]. shows the mechanism of action and criteria of each TNAs. TNAs are capable of targeting specific sequences of interest in the viral genome with a focus on the highly conserved sequence, such as targeting the highly conserved RNA-dependent RNA polymerase (RdRp) gene in the open reading frame 1ab (ORF1ab) region and the N gene by CRISPR-associated RNAs (crRNAs) deployed by the Cas13d system [35]. These antiviral therapeutics can inhibit viral gene expression [36] either during or after transcription [37]. Hence, nucleic acid-based therapeutics present great potential in combating SARS-CoV-2 infection. The most needed feature nowadays is scalable, rapid production; hence, nucleic acid-based therapeutics that possess this feature have the potential to be applied globally. Based on the published articles [38], we believe that mRNA vaccines, DNA vaccines, CRISPR, and ASO are more stable than the siRNA approach. Still, there have been no statistically significant comparative studies published to date. Despite that, we believe that the CRISPR systems will be more expensive and possibly harmful than all other approaches in the future. However, we think that ASO and mRNA would be the most cost-effective method.

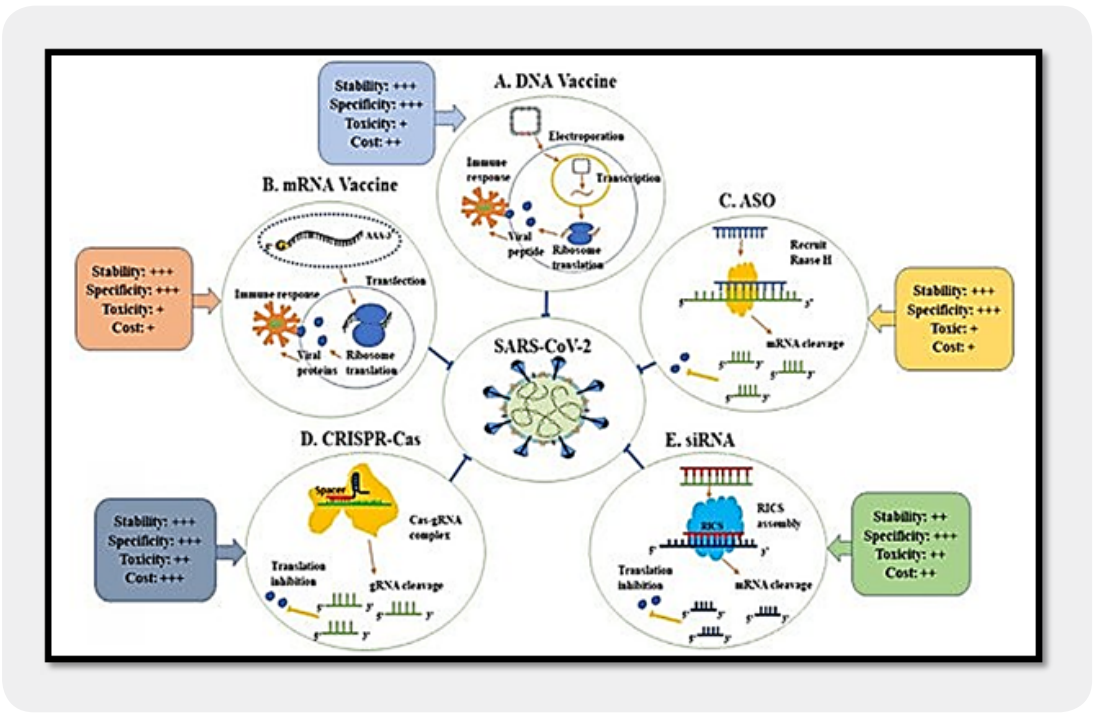


Figure: *Events during covid-19 malady*

Applications of therapeutic nucleic acids in the fight against SARS-CoV-2. (A) DNA vaccine: The SARS-CoV-2 S protein is contained within a circle of DNA, which serves as a DNA vaccine. Following electroporation, the permeation of the cell membrane will be increased, allowing DNA to enter the cytoplasm and so reach the nucleus more easily. Following then, DNA will be transcribed into mRNA, which will be further translated into the SARS-CoV-2 S protein and expressed on the cell membrane. (B) mRNA vaccine: The cytoplasmic integration of nanoparticle-encapsulated mRNA expressing the SARS-CoV-2 antigen will take place. The S protein mRNA utilizes the ribosome and bases to translate S proteins, which are expressed on the cell membrane. Immune cells will recognize the membrane S protein, which will result in the activation of an immune response. (C) ASO: ASO attaches to the complementary sequence of an mRNA in the nucleus. Following an RNA–DNA hybrid, which becomes a substrate for RNase H, the complementary base pairing between ASO and mRNA results in endonuclease-mediated transcript suppression. The transport of mRNA into the cytoplasm is inhibited, blocking protein synthesis. (D) CRISPR–Cas: Upon entering the cell, the Cas protein and the gRNA are both expressed, and the Cas protein and the gRNA form a complex with one another. In this way, the spacer region serves as a guide for the Cas effector by matching to complementary sequences in the viral genome, allowing the associated Cas effector to cleave the viral RNA and disrupt viral functions. (E) siRNA: The RISC recognizes and loads the siRNAs, which then separates two strands of associated siRNAs and releases the sense strands. In addition, the antisense strand associated with the RISC directs the complex to the target matching RNA sequences, which could host cellular transcripts or viral RNAs, ultimately leading to RNA degradation mediated by the RISC enzyme. As a result, these siRNAs have the potential to downregulate the expression of the target host/viral genes that are critical for viral activity and to disrupt viral replication and transcription [152,156,157,158,159]. One plus (+) indicates the lowest level, while three pluses (+++) indicate the highest level; these data were compiled from several articles [152,156,157,158,159]. Abbreviation: CRISPR, Clustered Regularly Interspaced Short Palindromic Repeats; Cas, CRISPR-associated; ASO, antisense oligonucleotides; RISC, RNA-induced silencing complexes; siRNA, small interfering RNA; gRNA, guide RNA.

JPM | Free Full-Text | Nucleic Acid-Based COVID-19 Therapy Targeting Cytokine Storms: Strategies to Quell the Storm | HTML (mdpi.com)

mRNA vaccines are considered one of the promising nucleic acid-based therapeutics due to their high potency, rapid, cheap manufacturing, and safe administration features. Their manufacturing does not involve any living part of the organism; it is either conventional via in vitro transcription of plasmid DNA and adding a cap analog and a poly(A) tail or derived from alphavirus RNA replication to form self-amplifying mRNA (SAM) vaccines [220]. mRNA vaccines are synthesized in vitro from a DNA template to express the intended antigen in host. The intended potent immune response is developed as mRNA is delivered to the host cell cytoplasm and encodes the desired antigen (Figure 5) [220]. mRNA vaccines have priority over conventional vaccines in many aspects, such as repeated administration [222] and safety concerns of conventional vaccines, especially live-attenuated vaccines, to cause infection. In contrast, mRNA degradation in the cell reduces the potential risk of infection. The enhancement ability of the introduced mRNA structure promotes the antibody lifespan, translation efficacy, flexibility, and neutralizing antibodies potency with just two doses. Therefore, mRNA vaccines offer scalable, rapid manufacturing with little platform altering / and

a fast-responding strategy to overcome the current pandemic dilemma /Unfortunately, these vaccines still have some drawbacks, such as the need to store in extremely low temperatures, which hinders transportation (cold chain challenges) and storage, which can be slightly reduced via encapsulation with LNPs, escape immune system recognition via viral envelope glycosylation, and possible side effects such as local and systemic inflammatory responses, Ultimately, mRNA vaccines still hold one of the keys to stop the SARS-CoV-2 infection.

Conclusions

Vaccinating hundreds of millions of people using COVID-19 mRNA vaccines will provide much-needed data on non-viral RNA delivery (especially with the utilization of LPN) and the immune response, safety, and effectiveness of this type of vaccine. Researchers may use these findings to execute an efficient approach by integrating siRNAs, miRNA mimics, antagomirs, or even genes in the same or comparable lipid nanoparticles used in vaccines for therapeutic applications (including regenerative medicine) and gene therapy in the future. Among the TNA-based approaches, miRNAs hold great potential in attenuating the cytokine storm with versatility and high efficiency. Multiple miRNAs in the host or SARS-CoV-2-encoded are associated with COVID-19 infection, where some might even inhibit the immune system. As such, the cytokine storm can be suppressed via targeting the associated miRNAs. Therefore, TNAs, especially miRNA therapeutics, hold the key to quell the cytokine storm and tackling COVID-19. The promising results with the COVID-19 vaccines offer a chance to fulfil the failed initial promise of gene therapy, which aimed to revolutionize molecular medicine while also moving away from viral-based gene delivery. Given the importance of vaccines in the future prevention of coronavirus-related illnesses, several novel techniques are currently in place that is encouraging. It is worth noting that without the earlier preclinical and clinical studies demonstrating the effectiveness of lipid nanoparticles as RNA delivery vehicles, these COVID-19 vaccines would not have been available in time to stop the pandemic.

Quest for Remedy Cytokine Storms

Some of these candidate JAK inhibitors also have the potential to address the concern underlying the use of JAK inhibitors on host antiviral and antibacterial immunity responses. For example, BMS-986165 and PF-06826647, TYK2 selective inhibitors currently in Phase II clinical trials for psoriasis [39] (Clinical Trial Numbersii: NCT03881059 and NCT03895372) (Figure 1), can be tested in COVID-19. These inhibitors would potentially not interact with the Type II IFN response (IFNγ) necessary in antibacterial immunity but still inhibit other cytokines in COVID-19. Similarly, potential JAK3-specific inhibitors, such as decernotinib (VX-509), currently in a Phase II clinical trial for RA [40] (Clinical Trial Number: NCT01590459) and ritlecitinib (PF-06651600iii) (Figure 1), currently in a Phase III clinical trial for alopecia areata (Clinical Trial Number: NCT04006457) can also be tested against COVID-19 either as monotherapy or in combination with IL-6/IL-6R antagonists. These JAK inhibitors can be expected to not interact with both Type I and Type II IFN-mediated antibacterial and antiviral responses, a concern when using pan-JAK inhibitors currently in clinical trials for COVID-19. Such immunosuppressive therapies may be limited by the side effects and contraindication to some of these regimes, which emphasizes the need to identify the patients who benefit most from such treatments, as discussed earlier [41].

Bibliography

1. Girija, A. S. S., Shankar, E. M. & Larsson, M. (2020). Could SARS-CoV-2-induced hyperinflammation magnify the severity of coronavirus disease (Covid-19) leading to acute respiratory distress syndrome? *Front Immunol., 11,* 1206.

2. Staats, P., Giannakopoulos, G., Blake, J., Liebler, E. & Levy, R. M. (2020). The use of non-invasive vagus nerve stimulation to treat respiratory symptoms associated with COVID-19: A theoretical hypothesis and early clinical experience. *Neuromodulation, 23*(6), 784-788.

3. Wang, D., *et al*. (2020). Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA., 323*(11), 1061-1609. 24.

4. Aggarwal, G., *et al.* (2020). Association of cardiovascular disease with coronavirus disease 2019 (COVID-19) severity: a meta-analysis. *Curr Probl Cardiol., 45*(8), 100617.

5. Verdecchia, P., *et al*. (2020). The pivotal link between ACE2 deficiency and SARSCoV-2 infection. *Eur J Intern Med., 76,* 14-20.

6. Jin, G. Y., Jin, L. L., Zheng, J. & He, B. J. (2020). Advantages of anti-inflammatory acupuncture in treating sepsis of novel coronavirus pneumonia. *World J Tradit Chin Med., 6*(2), 188-195.

7. Herold, T., Jurinovic, V., Arnreich, C., *et al*. (2020). Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. *J Allergy Clin Immunol., 146*(1), 128-136.

8. Liu, F., Li, L., Xu, M., *et al.* (2020). Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. *J Clin Virol., 127,* 104370.

9. Mai Abdel Haleem Abusalah, Moad Khalifa, Mohammad Al-Hatamleh, A. I., Mu'taman Jarrar, Rohimah Mohamud & Yean Yean Chan (2022). Nucleic Acid-Based COVID-19 Therapy Targeting Cytokine Storms: Strategies to Quell the Storm. *J. Pers. Med., 12*(3), 386.

10. Hertanto, D. M., Wiratama, B. S. & Sutanto, H. (2021). Immunomodulation as a Potent COVID-19 Pharmacotherapy: Past, Present and Future. *Journal of Inflammation Research, 14,* 3419-3428l.

11. Kulkarni, S., Fisk, M., Kostapanos, M., *et al.* (2020). Repurposed immunomodulatory drugs for Covid-19 in pre-ICu patients - mulTi-arm therapeutic study in pre-ICu patients admitted with Covid-19- repurposed drugs (TACTIC-R): a structured summary of a study protocol for a randomised controlled trial. *Trials, 21*(1), 626.

12. (2020). Coronavirus | Scientists break down three stages of infection, suggest individualised treatment for patients.

13. a) Neufeldt, C. J., Cerikan, B., Cortese, M., *et al*. (2022). SARS-CoV-2 infection induces a pro-inflammatory cytokine response through cGAS-STING and NF-κB. *Commun Biol., 5*(1), 45.

b) Onomoto, K., Onoguchi, K. & Yoneyama, M. (2021). Regulation of RIG-I-like receptor-mediated signaling: interaction between host and viral factors. *Cell Mol Immunol., 18,* 539-555.

14. a) Rodrigues, T. S., de Sa, K. S. G., Ishimoto, A. Y., *et al*. (2021). Inflammasomes are activated in response to SARS-CoV-2 infection and are associated with COVID-19 severity in patients. *J Exp Med., 218*(3).

b) Toldo, S., Bussani, R., Nuzzi, V., *et al*. (2021). Inflammasome formation in the lungs of patients with fatal COVID-19. *Inflamm Res., 70*(1), 7-10.

15. Harrell, C. R., Jovicic, B. P., Djonov, V., Volarevic, V. & Amantini, C. (2020). Therapeutic potential of mesenchymal stem cells and their secretome in the treatment of SARS-CoV-2-induced acute respiratory distress syndrome. *Anal Cell Pathol., 2020,* 1939768.

16. Keshavarzi Arshadi, A., Webb, J., Salem, M., Cruz, E., Calad-Thomson, S., Ghadirian, N., *et al.* (2020). Artificial Intelligence for COVID-19 Drug Discovery and Vaccine Development. *Front. Artif. Intell., 3,* 65.

17. Milken Institute (2021). COVID-19 Treatment and Vaccine Tracker. 2020.

18. INOVIO. INOVIO's Pan-COVID-19 Vaccine Candidate (INO4802) Induces Broad Immunity Against Major Viral Variants in Preclinical Studies.

19. a) Han, H., Ma, Q., Li, C., Liu, R., Zhao, L., Wang, W., *et al.* (2020). Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. *Emerg. Microbes Infect., 9*(1), 1123-1130.

b) Liu, B. M., Martins, T. B., Peterson, L. K. & Hill, H. R. (2021). Clinical significance of measuring serum cytokine levels as inflammatory biomarkers in adult and pediatric COVID-19 cases: A review. *Cytokine, 142,* 155478.

20. McElvaney, O. J., McEvoy, N. L., McElvaney, O. F., Carroll, T. P., Murphy, M. P., Dunlea, D. M., *et al.* (2020). Characterization of the inflammatory response to severe COVID-19 illness. *Am. J. Respir. Crit. Care Med., 202*(6), 812-821.

21. Ragab, D., Salah Eldin, H., Taeimah, M., Khattab, R. & Salem, R. (2020). The COVID-19 cytokine storm, what we know so far. *Front. Immunol., 11,* 1446.

22. Panigrahy, D., Gilligan, M. M., Huang, S., Gartung, A., Cortés-Puch, I., Sime, P. J., *et al*. (2020). Inflammation resolution: A dual-pronged approach to averting cytokine storms in COVID-19? *Cancer Metastasis Rev., 39*(2), 337-340.

23. Bhaskar, S., Sinha, A., Banach, M., Mittoo, S., Weissert, R., Kass, J. S., *et al.* (2020). Cytokine storm in COVID-19-immunopathological mechanisms, clinical considerations, and therapeutic approaches: The REPROGRAM consortium position paper. *Front. Immunol., 11,* 1648.

24. Chen, G., Wu, D., Guo, W., Cao, Y., Huang, D., Wang, H., *et al.* (2020). Clinical and immunological features of severe and moderate coronavirus disease 2019. *J. Clin. Investig., 130*(5), 2620-2629.

25. Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., *et al.* (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *Lancet, 395*(10229), 1054-1062.

26. Hirano, T. & Murakami, M. (2020). COVID-19: A new virus, but a familiar receptor and cytokine release syndrome. *Immunity, 52*(5), 731-733.

27. Liu, B., Li, M., Zhou, Z., Guan, X. & Xiang, Y. (2020). Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? *J. Autoimmun., 111,* 102452.

28. Francesco Colotta, Fabio Re, Nadia Polentarutti, Silvano Sozzani & Alberto Mantovani (1992). Modulation of Granulocyte Survival and Programmed Cell Death by Cytokines and Bacterial Products. *Blood, 80*(8), 2012-2020.

29. Meredith Wadman, Jennifer Couzin-Frankel, Jocelyn Kaiser & Catherine Matacic (2020). How does coronavirus kill? Clinicians trace a ferocious rampage through the body, from brain to toes. *Science, 368*(6489), 356-360.

30. Ricardo Jose, J. & Ari Manuel (2020). COVID-19 cytokine storm: the interplay between inflammation and coagulation. *The Lancet Respir Med., 8*(6), e46-e47.

31. Shimon Shatzmiller, *et al.* (2020). Cytokine Storm: A Coronavirus Complication. *CPQ Microbiology, 3*(6), 01-07.

32. One-stop Cytokine Release Syndrome (CRS) Management Solutions.

33. Le, T. K., Paris, C., Khan, K. S., Robson, F., Ng, W. L. & Rocchi, P. (2021). Nucleic acid-based technologies targeting coronaviruses. *Trends Biochem. Sci., 46*(5), 351-365.

34. Abbott, T. R., Dhamdhere, G., Liu, Y., Lin, X., Goudy, L., Zeng, L., *et al.* (2020). Development of CRISPR as an antiviral strategy to combat SARS-CoV-2 and influenza. *Cell, 181*(4), 865-876.

35. Sridharan, K. & Gogtay, N. J. (2016). Therapeutic nucleic acids: Current clinical status. *Br. J. Clin. Pharmacol., 82*(3), 659-672.

36. Gewirtz, A. M., Sokol, D. L. & Ratajczak, M. Z. (1998). Nucleic acid therapeutics: State of the art and future prospects. *Blood, 92*(3), 712-736.

37. a) Yan, Z. P., Yang, M. & Lai, C. L. (2021). COVID-19 Vaccines: A Review of the Safety and Efficacy of Current Clinical Trials. *Pharmaceuticals, 14*(5), 406.

b) Dash, P., Mohapatra, S., Ghosh, S. & Nayak, B. (2020). A Scoping Insight on Potential Prophylactics, Vaccines and Therapeutic Weaponry for the Ongoing Novel Coronavirus (COVID-19) Pandemic- A Comprehensive Review. Front. Pharmacol., 11, 590154.

c. Flanagan, K. L., Best, E., Crawford, N. W., Giles, M., Koirala, A., Macartney, K., *et al.* (2020). Progress and Pitfalls in the Quest for Effective SARS-CoV-2 (COVID-19) Vaccines. *Front. Immunol., 11,* 579250.

d. Berber, B., Aydin, C., Kocabas, F., Guney-Esken, G., Yilancioglu, K., Karadag-Alpaslan, M., *et al.* (2021). Gene editing and RNAi approaches for COVID-19 diagnostics and therapeutics. *Gene Ther., 28*(6), 290-305.

38. Nogueira, M., Puig, L. & Torres, T. (2020). JAK Inhibitors for Treatment of Psoriasis: Focus on Selective TYK2 Inhibitors. *Drugs, 80*(4), 341–352.

39. Delgoffe, G. M. & Vignali, D. A. A. (2013). STAT heterodimers in immunity: a mixed message or a unique signal? *JAK STAT., 2*(1), e23060.

40. Wei Luo, Li-Jun Jiang, Qian Chen, Tao Wang & Da-Wei Ye (2020). Targeting JAK-STAT Signaling to Control Cytokine Release Syndrome in COVID-19. *Trends in Pharmacological Sciences, 41*(8), 531-543.