Management of Spike Protein-Related Pathology

Subjects: Infectious Diseases

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In the wake of the COVID-19 crisis, a need has arisen to prevent and treat two related conditions, COVID-19 vaccine injury and long COVID-19, both of which can trace at least part of their aetiology to the spike protein, which can cause harm through several mechanisms. One significant mechanism of harm is vascular, and it is mediated by the spike protein, a common element of the COVID-19 illness, and it is related to receiving a COVID-19 vaccine. Given the significant number of people experiencing these two related conditions, it is imperative to develop treatment protocols, as well as to consider the diversity of people experiencing long COVID-19 and vaccine injury.

long COVID COVID-19 vaccine injury spike protein thrombosis

1. Introduction

According to available data, by 30 September 2022, 68% of the world's population had received at least one dose of the COVID-19 vaccine, and 12.74 billion doses had been administered [1]. The vaccines most commonly administered were Comirnaty (Pfizer/BioNTech), Covishield (Astrazeneca), CoronaVac (Sinovac), Spikevax (Moderna), and Jcovden (Johnson & Johnson) [2]. Of these, approximately 30% of the doses produced by 22 January 2022 were in the form of a novel vaccine with a synthetic N1-methyl-pseudoiridinylated mRNA encapsulated in a lipid nanoparticle (LNP) [3].

LNPs are a new technology that was not used in vaccine delivery until the emergency use authorization (EUA) of the Pfizer/BioNTech BNT162b2 and Moderna mRNA-1273 COVID-19 vaccines [4]. This was also unprecedented in the approval process, being the fastest for any vaccine [5], leaving many concerns with regard to long-term safety [6], which was difficult to evaluate due to the unblinding of the initial clinical trials [7].

Whilst the delivery technology of LNPs have previously been used to deliver small molecules, it has only recently been used to deliver RNA. LNPs are advantageous for targeting brain tissue, as they can cross the blood–brain barrier (BBB) [8][9]. The first drug used and LNP to deliver RNA was a small interfering RNA (siRNA)-based drug, known as Onpattro (Alnylam Pharmaceuticals), first approved in 2018 for the treatment of polyneuropathies [10].

Given both the novelty of the technology and the paucity of data on which approval was based (which was also subject to data integrity issues [11]), long-term effects cannot be definitively ruled out, especially because many of the foundational claims on which approval was based have been contested by recent experiments [12][13][14]. For example, in contrast to claims that the injection stayed at the injection site [15], and that spike protein would only be

expressed for a short period of time (based on the lability of non-pseudouridylated RNA [16]), the contents and products of the COVID-19 vaccines have been found in the blood stream of most vaccinees studied within hours to days [12].

The first claim was based on Intramuscular administration [15], and the second claim was based on the lability of RNA [17], with a typical RNA half-life of minutes [18]; however, biodistribution studies have found significant expression of spikes in other tissues and organs [12], and researchers have found both vaccine mRNA and spike protein (which is encoded by the vaccine sequence) two months post-administration [14], and even up to four months post-vaccination [13]. One preprint study of people with SARS-CoV-2 negative post-vaccination Long COVID-19-like symptoms showed spike protein persistence, on average, 105 days post vaccination [19]. Long COVID-19 patients (post SARS-CoV-2 infection) show spike protein persistence up to 15 months [20]. Another study showed spike protein persistence in the gut of long COVID-19 patients, but not in the bloodstream.

Spike proteins can be packaged in exosomes [13], possibly resulting in inflammation and immune activation [21][22] in organs and tissues distant from the injection site [13]. Extracellular vesicles are capable of crossing the blood–brain barrier [23], and LNPs, as well as exosomes, will exchange more readily in small diameter vessels with low flow rates (i.e., capillaries and small vessels) [24]. Importantly, the spike protein seems to additionally impact blood–brain barrier permeability [25][26]. These results challenge the initial mechanistic foundation on which the presumption of safety is contingent.

Compared with other vaccines, COVID-19 vaccines have a much higher adverse event rate [27]. Histopathological findings and autopsies of those dying post-vaccination support the causative role of the vaccine in deaths [28], most commonly from vascular-related events. Pharmacovigilance programs in several countries have observed a safety signal for myocarditis in the COVID-19 vaccinated population [29][30][31]. A US survey found that 19% of myocarditis cases had not recovered at 90 days after onset [32]. In addition, screening of BNT162b2 vaccine recipients among boys aged 13–18 in a Thai study revealed that 2.3% of the boys had at least one elevated cardiac biomarker or positive lab assessment, and 29% had at least one cardiac manifestation, such as tachycardia, palpitation, or myopericarditis [33]. Given this information, and given the ubiquitous use of COVID-19 vaccines, it is possible that widespread subclinical damage exists in the COVID-19 vaccinated population. Structurally, the spike protein, particularly the receptor-binding domain (RBD) of the S1 subunit, has attracted much attention, as it is the most prominent aspect of the viral capsid [34] (It consists of spike (S) and nucleocapsid (N)) glycoproteins. Cell entry is mediated by the binding of Spike RBD to the Angiotensin Converting Enzyme II (ACE2) [35]. Therefore, by preventing this binding through allosteric inhibition, it is possible to prevent the entry of SARS-CoV-2 virions into the cell and subsequent infection [36].

2. Pathophysiology

2.1. Mechanisms of Harm

As mentioned previously, while it was expected that the LNP-encapsulated synthetic mRNAs would remain at the injection site and rapidly degrade, there is substantial evidence that they enter the bloodstream [37], deposit in other tissues [38], and even in the breast milk of lactating mothers [39]. The S1 subunit of the spike protein can damage the endothelial lining of blood vessels [40][41][42]. Vaccine particles in the bloodstream can cause a significant inflammatory response in blood vessels [43].

Several hypotheses for the mechanisms of long COVID-19 exist, including immune dysregulation, auto-immunity, endothelial dysfunction, activation of coagulation, and latent viral persistence [44][45]. Cardiovascular complications, particularly microthrombus formation, feature both in the etiologies of long COVID-19 [46][47] as well as COVID-19 vaccine injury [48].

The SARS-CoV-2 (infection or vaccine produced) spike protein can bind to the ACE2 receptor on platelets, leading to their activation [49], and it can cause fibrinogen-resistant blood clots [50]. Spike protein fragments can also be amyloidogenic on their own [51]. Several reports demonstrate elevated troponin levels in cardiac symptoms following the COVID-19 vaccine [52].

2.2. Clinical Observations

Although no official definition exists for ‘post-COVID-19-Vaccine Syndrome,’ a temporal correlation between receiving a COVID-19 vaccine and the beginning or worsening of a patient’s clinical manifestations is sufficient to make the diagnosis of a COVID-19 vaccine-induced injury when the symptoms are unexplained by other concurrent causes. It should, however, be recognized that there is a significant overlap between the symptoms and features of the long COVID-19 syndrome [53] and the post-COVID-19-Vaccine Syndrome [54]. However, a number of clinical features appear to be distinctive of the post-COVID-19 vaccine syndrome; most notably, severe neurological symptoms (particularly small fiber neuropathy) appears to be more common following vaccination [55][56][57]. To complicate matters further, patients with long COVID-19 are often vaccinated [58], making the issue of definition more difficult.

Unfortunately, only post mortem examination to date can prove causal relationship when tissues damaged demonstrate the presence of spike protein and absence of nucleocapsid protein (SARS-CoV-2 only) [59].

The true magnitude of post-COVID-19-Vaccine Syndrome is unknown, as data are limited to short duration clinical trials. From a survey of vaccinated individuals, approximately 1% required medical attention immediately following vaccination [60]. A nationwide cohort study of U.S. veterans reported adverse reactions in 8.5% of recipients of the Pfizer vaccine and 7.9% of those receiving the Moderna vaccine [61].

3. Therapeutic Interventions

There are several non-specific means of counteracting the effects of long-COVID-19 and post-COVID-19 vaccine injury. These include nutritional support for general immune regulation and for overall health [62], as well as more

specific, spike protein-specific therapeutics.

Non-specific therapeutic moieties include nutritional optimization, as diet-related pathologies, including obesity [63] and type 2 diabetes [64], were associated with worse outcomes from COVID-19 infection. Additionally, high blood glucose facilitates several steps of the viral lifecycle and infection progression [65], motivating the reduction in sugar and refined carbohydrate intake, which are associated with increases in blood sugar. Furthermore, adoption of a whole-food, plant-based diet is associated with decreased oxidative stress and inflammation [66] and better cardiovascular conditions. These positive impacts are attributed to their nutrient profiles, consisting of antioxidants, vitamins, minerals, and phytochemical-containing phenolic compounds, which can exert antioxidant, anti-inflammatory, and other beneficial effects [67][68].

The microbiota plays a fundamental role in the induction, training, and function of the host's immune system and thus shape the responses to its challenges [69]. Gut microbiome composition was significantly altered in patients with COVID-19 compared with non-COVID-19 individuals, irrespective of whether patients had received medication [70]. The researchers said patients with severe illness exhibit high blood plasma levels of inflammatory cytokines and inflammatory markers. Additionally, given altered gut microbiota composition in SARS-CoV-2 infected subjects, there is substantial involvement of the GI tract during infection. These results suggest that gut microbiota composition is associated with the magnitude of immune response to COVID-19 and subsequent tissue damage and thus could play a role in regulating disease severity. The scientists also found that, because a small subset of patients showed gut microbiota dysbiosis, or imbalance, even 30 days after recovery, this could be a potential explanation for why some symptoms persist in long COVID-19 [71].

Given the intricate influence of gut microbiota (GM) on host immune effectors and subsequent inflammatory profile, GM composition and function might contribute to explaining the individual resilience/fragility with respect to COVID-19 and/or the response to therapeutics (vaccines), which deserve further research [72]. Microbial diversity can be improved by consuming many prebiotics and probiotics, such as sauerkraut and kimchi.

The design and discovery of spike protein inhibitors have followed a typical drug repurposing process. Given the structural similarity of the SARS-CoV-2 spike protein to other coronaviruses [73][74], compounds that work for these could potentially be repurposed for SARS-CoV-2 spike inhibition.

Typically, once a prospective compound for repurposing has been identified, it is tested using a ligand-binding assay (LBA) [75]. These assays can provide information on binding affinity and kinetics, as well as binding stoichiometries and even cooperative effects [75].

The next level of verification may be an in vitro assay for viral inhibition in cell culture, where cells are infected with a virus, and viral levels or titre (concentration) are measured by counting viral plaques [76] or measuring viral nucleic acid (NA) levels [77]. Control cells are compared with treated cells. Though the approach has limitations, in not considering the whole-body dynamics of a virus [78], it can serve as a useful starting point.

In vivo studies are a further level of verification, which show the impact of the intervention in an animal model. Beyond in vivo studies, there are clinical studies, which are typically of two design types: observational and randomized control trials (RCTs) [79].

3.1. Establishing a Healthy Microbiome

The state of the microbiome is an essential criterion for the progression of acute COVID-19 infection, long COVID-19, and post vaccine syndrome [80][81][82][83][84]. Patients with post-vaccine syndrome classically have a severe dysbiosis with loss of Bifidobacterium [85][86][87]. A whole-food, plant-based diet may improve outcomes in COVID-19 [88][89][90], and people following plant-based diets, on average, experienced less severe COVID-19 symptoms [91]. Dietary sources of probiotics include fermented dairy [92], chia seeds [93], glucomannan [94][95], and supplements [96].

3.2. Preventing Spike Protein Damage

Inhibiting Spike Protein Cleavage

The furin cleavage site on SARS-CoV-2 has been suggested as a reason for its increased infectivity relative to SARS-CoV [97], which had a higher fatality rate, which was much less infectious [98]. Cleavage of the full-length spike protein into S1 and S2 subunits is essential for SARS-CoV-2 entry into human lung cells [99][100][101][102]. The full-length spike is present in both SARS-CoV-2 infection, as well as vaccination, and it is the only protein common to SARS-CoV-2 infection and vaccination (it is the only protein present in vaccination) [103].

Vaccine-produced spike has an important difference as compared to the SARS-CoV-2 spike—the inclusion of two proline mutations to stabilize the pre-fusion state of the spike protein. These are related to Pfizer's BNT162b2 [104], Moderna's mRNA-1273 [105], Johnson & Johnson's Ad26.COV2.S [106], and NovaVax's NVAX-CoV2373 [107]. This was first discovered in the context of MERS [108]. Other vaccines apparently encode the full-length, wild-type spike protein, including AstraZeneca's ChAdOx1 [109] and SinoVac's CoronaVac [110].

These dual proline mutations featured in the mRNA vaccines stabilize the pre-fusion state, though some cleavage still occurs [108][111][112], and, interestingly, the mutations produce an unknown cleavage product of 40 kDa, where typical cleavage products for the wild-type spike protein are 80 kDa [112]. As such, targeting the cleavage of spike protein is likely to make a difference in long COVID, as well as vaccine injury from the vaccines encoding the full-length wild-type spike protein (AstraZeneca, SinoVac and others), though this may have less of an impact in vaccines encoding the pre-fusion-stabilized spike protein (Pfizer, Moderna, Johnson & Johnson, NovaVax and others).

3.3. Inhibiting Spike Protein Binding

One of the most direct therapeutic mechanisms is to seek compounds which disrupt the ACE2/Spike interface, either through binding ACE2 or spike in isolation, or disrupting the interface itself. This problem is a steric and

conformational problem, for which computational prediction using structural models is highly amenable. A great many computational studies of the spike protein and ACE2 binding compounds have been performed, and some of these hits have further been developed through LBAs, in vitro studies, in vivo studies in animal models, and, lastly, clinical trials with human subjects. Few of the compounds reach the final stage, though several with this mechanism of action have been investigated. Most promising were ivermectin and quercetin, as computational prediction showed these bind to the spike. If the spike is bound in the receptor binding domain (RBD), the interaction with ACE2 receptors, by which spike protein exerts its inflammatory effect, is also inhibited.

3.4. Clearing Spike Protein

Importantly, to progress beyond this, it is necessary to clear out the spike protein. This can be accomplished through upregulation of the protein degradative pathways in the body through upregulation of autophagy. Autophagy can be upregulated by fasting [113] and calorie restriction [114], especially if protein is reduced [115]. Autophagy in many instances does not require the complete cessation of food intake (protocols are available at https://COVID19criticalcare.com/treatment-protocols/, accessed on 15 April 2023). Sharply decreasing protein intake can upregulate autophagy pathways [116], and this can be accomplished while still eating, which makes this more approachable as a protocol. Regular fasting was also associated with better outcomes from acute COVID-19 [117].

3.5. Healing the Damage

After the damage process has been attenuated, it is necessary to heal the damage that has occurred. The healing stage requires normalizing the immune response, reducing lingering inflammation (such as by targeting interleukin 6 [118]), and addressing any acute damage in affected tissues, particularly cardiovascular damage [46][47][48]. Damage reduction may also mean reducing the level of blood clotting if clotting is present and repairing any organ damage, if relevant. The stage of healing requires normalizing the immune response, reducing lingering inflammation (such as by targeting interleukin 6 [118]), and addressing any acute damage in whatever affected tissues, which, for the purposes, includes blood. Micro-clots are a possible etiological factor in long COVID-19 [119][120][121], as well as COVID-19 vaccine injury [122]. Damage reduction may also mean reducing the level of blood clotting if clotting is present, and repairing any organ damage, if relevant. Sufferers of long COVID-19 have been found to have a higher inflammatory response to the initial COVID-19 infection than those who recover completely from COVID-19 [123], so anti-inflammatory and immunomodulatory medications have been identified as potential long COVID-19 therapeutics.

Anti-coagulant medication, such as aspirin, can be useful in alleviating the cardiovascular complications of COVID-19 [124][125], as they have a long history of use in improving blood flow and reducing coagulopathies [126][127][128].

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