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Review Article

Long Covid and Serious Side Reactions to mRNA-Based Vaccines (VSITV) Are Mainly Spike Protein-Induced Thrombotic Vasculitis

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Abstract:

Long COVID syndrome, known as Long COVID, refers to a series of debilitating symptoms that arise after infection with the SARS-CoV-2 virus. These symptoms are similar to those experienced by some people after vaccination with vaccines based on mRNA platforms (Pfizer, Moderna). With more than 200 million Long COVID patients worldwide and an increase in cases of moderate to severe reactions after administration of mRNA vaccines (VSITV), the effects on quality of life and economics are significant, for what is necessary to pay urgent attention to understand its pathophysiology and to provide an adequate diagnosis and treatment.

In this article, we describe our perspective that both Long COVID and common side effects of mRNA vaccines (VSITV) induce persistent and prolonged expression of the spike protein (SPIKE) in various tissues and organs of the body. This would induce coagulopathy, microscopic vasculitis, and endothelitis as the main drivers of the disease, and may also cause or worsen other common pathologies in Long COVID, such as mast cell activation syndrome, dysautonomia, and sudden deaths due to arrhythmias and heart attacks, reports of which continue to rise.

Given that the SARS-CoV-2 spike protein can independently induce fibrinoid microclot formation, platelet activation, and endothelitis, we predict that the persistence of the spike protein will be a key mechanism driving ongoing coagulopathy in Long COVID and in the VSITV. We discuss various treatment goals to address coagulopathy, endothelitis, and vasculitis and predict that treatment, especially if given early, with a combination of anticoagulants, antiplatelets, corticosteroids, and rapamycin/everolimus, will provide significant relief for many patients.

To focus attention on these treatment targets, we propose that the term Long COVID be changed to "natural Spike Protein-Induced Thrombotic Vasculitis" (NSITV) and that serious side effects of mRNA vaccines be renamed "Vaccine Spike Protein - Induced Thrombotic Vasculitis" (VSITV). Are mainly due to a persistent and disseminated cellular expression of the Spike protein". These ideas require urgent testing, especially as the world tries to live with COVID-19.

Key words: long covid; mRNA vaccines side effects; immunothrombosis; spike protein

Introduction

Long COVID (or the post-acute sequelae of COVID-19) is a debilitating multisystem disease that causes significant disability [1]. The World Health Organization [2] has defined Long COVID as those cases in which a probable or confirmed infection by SARS-CoV-2 occurs, with onset of symptoms within three months, a duration of at least two months and no alternative diagnosis. It is estimated that Long COVID affects more than 200 million people worldwide, with most cases considered "mild" [3,4] and even a third of them are asymptomatic [5,6]. In addition, a significant increase in the presentation of prolonged COVID-19-like symptoms (VSITV) has been observed after SARSCoV-2 vaccination, especially with mRNA- based vaccines [7–11].

Patients with Long COVID experience on average 56 symptoms affecting nine different body systems [1], the most common being fatigue, cognitive dysfunction, dyspnea, exercise intolerance, exacerbation of symptoms after exertion (PESE), sleep disorders and myalgias [1,3,12–14]. Given this broad definition, Long COVID is likely to be a multipathology disease [10–12].

Estimates of the long-term prevalence of COVID-19 vary [3,13,18,19], but studies in Scotland have shown that it affects 1.8-3.2% of the

population [20,21], in compared with cancer (2.5%), chronic kidney disease (3.2%), chronic obstructive pulmonary disease (2.3%), and stroke (2.2%) [22]. Two meta-analyses have shown persistent symptoms in 43-45% of patients after the acute phase of COVID-19 [3,13]. Follow-up studies suggest that 85% of patients presenting with symptoms two months after infection remain symptomatic at one year [23]. Similarly, resolution of symptoms after 90 days appears to be rare [24], leading to disability in a previously economically active population [1]. Consequently, the economic costs are estimated to be as high as $25 billion in the UK alone [25].

In addition to its modest benefits in acute cases of COVID-19, vaccination provides a modest reduction in the odds of developing Long COVID (13% and 9% reduction after the first and second doses, respectively [26]). However, other investigations have shown that each SARS-CoV-2 reinfection increases the risk of death, hospitalization, and/or multi-organ complications, regardless of vaccination status [27]. Therefore, the protections provided by vaccination appear to be far from absolute, especially when many public health measures are being scaled back in various countries [28–30]. As a result, the prevalence of Long COVID continues to increase [31]. In addition, both the severity and type of side reactions to mRNA-based vaccines are increasing, as is the diversity of clinical manifestations and affected organs, from sudden death in healthy young people, including athletes, to myocarditis, endomyocarditis, pericarditis, venous and arterial thrombosis, meningoencephalopathies, peripheral neuropathies, systemic inflammatory syndromes such as Still's disease, gastrointestinal syndromes, and infertility due to orchitis (decreased spermatocyte production) or premature ovarian failure due to oophoritis. The list of tissues and organs affected so far is extensive (you can review the report "The Frequency and Associations of Adverse Reactions of COVID-19 Vaccines Reported to Pharmacovigilance Systems in the European Union and the United States. Supplementary file").

It is therefore evident that the majority of Long COVID and VSITV cases do not resolve over time, and their prevalence continues to rise, carrying significant economic costs for a previously productive workforce. Therefore, understanding the pathophysiology of Long COVID and VSITV is imperative, and treatments must be urgently implemented.

Vaccines based on mRNA platforms: the foundations that support VSITV

As of this writing, the following is indisputable regarding vaccines based on mRNA platforms:

1. After administration of the vaccine, the mRNA spreads in various tissues and cells begin to express the spike protein (SPIKE) encoded by the mRNA in different organs and tissues.
2. The expression of the spike protein in cells can last longer than initially reported, reaching months and even years.
3. The widespread expression and duration of spike protein in various organs and tissues cannot be predicted or controlled with Pfizer and Moderna mRNA-based vaccines.
4. Like any foreign protein or antigen expressed in cells, spike protein triggers an antibody- and T-lymphocyte- mediated immune response that destroys cells producing and expressing spike protein, which in turn results in a systemic inflammatory process.
5. Expression of the spike protein encoded by mRNA vaccines in endothelial cells renders them susceptible to destruction, inflammation, and dysfunction, which can lead to vasculitis and coagulopathy characterized by microthrombosis and hyperactivation of platelets. These effects may be direct, inherent to the abnormal expression of the spike protein in the endothelium, or mediated by the immune response induced by the spike protein, or both mechanisms.
6. The specific immune response against the spike protein will persist as long as there are cells in the tissues and organs that produce it. The longer the spike protein is present, the longer the immune-mediated inflammation lasts, resulting in chronic damage to the tissues and organs that contain cells that produce the spike protein encoded by the mRNA vaccines.
7. Administration of booster doses of mRNA vaccines will induce stronger, faster, and longer immune responses, as well as increased spike protein expression in cells, resulting in increased risk of destruction and damage to tissues and organs.

Acute COVID-19: the foundations that support Long COVID-19

Endothelial cells play vital roles in vascular homeostasis and hemostasis, including regulation of vascular tone, blood flow, fibrinolysis, and platelet aggregation [32-35]. Acute COVID-19 appears to be primarily a disease of the vascular endothelium leading to microcirculatory thrombotic vasculitis [33,34,36–43]. SARS-CoV-2 spike proteins allow the virus to bind to target cells through binding to angiotensin-converting enzyme 2 (ACE2), followed by intracellular viral replication [42,44,45]. ACE2 is present in the tongue, nasal mucosa, and lungs as the initial portal of entry, and is also found in the vasculature on endothelial cells. This gives SARS-CoV-2 ample opportunity to spread easily throughout the body, including across the blood- brain barrier [33,34,37,42,46–48].

Entry of SARS-CoV-2 into endothelial cells reduces ACE2 expression, leading to a proinflammatory and prothrombotic environment [34,49–51]. Endothelial injury may be the result of direct SARS-CoV-2 infection, leading to endothelial cell apoptosis and endothelitis, as well as subsequent systemic immuno-inflammatory responses [33,34,37,39,49, 51,52].

Spike proteins change the structure of beta and gamma fibrinogen, complement 3, and prothrombin, resulting in the development of blood clots that are larger and more difficult to break down. Spike proteins can trigger clot formation in the blood even without thrombin and platelets. Spike protein alone can cause neuronal damage [53], destabilize microvascular haemostasis [54], induce thrombosis [55], (irreversibly) activate platelets [56–58] and alter endothelial function [43,59], with some effects not dependent on ACE2 [60] or possibly related to anti-spike antibodies [61]. Endothelial dysfunction results in impaired vascular tone and a prothrombotic state [32,34,35,37,43,49].

Post-mortem examination of critically ill patients with COVID-19 has revealed the presence of a generalized coagulopathy, with alveolar-capillary microthrombi nine times more frequent than in influenza A [62]. Furthermore, Pretorius et al. [40] found a significant microclot burden in acute patients with COVID-19, regardless of disease severity, compared with patients with type 2 diabetes and healthy controls. These microclots, of an amyloid nature, laid the foundation for the chronic sequelae following COVID-19.

Thrombi are known to develop from inflammation, partly due to platelet hyperactivation [63]. COVID-19 is a highly inflammatory disease, with the potential to trigger cytokine storms [64]. In fact, COVID-19 activates platelets and the complement system, causing endothelial dysfunction [43,65]. The resulting pro-inflammatory milieu can lead to a condition known as immunothrombosis, which especially affects the microvasculature [65]. In addition, the S1 subunit of the SARS-CoV-2 spike protein can directly interact with platelets and fibrin, causing microclot formation [36,56,66–68].

Specifically, the S1 subunit produces structural changes in β and γ fibrin (gene), complement 3, and prothrombin, resulting in the formation of extensive abnormal microclots [36,58,67–70]. These microclots appear to pathologically alter blood flow in systemic microcapillaries [36,71–73], including the brain [48], heart [73–75], lungs [46,73,76] and kidneys [73]. Microclots induced by spike protein are resistant to fibrinolysis, creating the potential for false-negative clot dissolving tests (such as D-dimer) [77] and making microclots persistent and central to pathogenesis of Long COVID and VSITV [36,69,78].

There are several proposed mechanisms that offer valid explanations for Long COVID. In many patients, it is possible that several of these pathologies coexist and interact with each other. Suggested ideas include mast cell activation syndrome (MCAS), neuroinflammation, viral reactivation, persistence of SARS-CoV-2 and/or spike protein, autoimmunity, and gut dysbiosis [9,79].

However, a pathology related to microclots, platelet hyperactivation, and endothelial dysfunction is being increasingly recognized [36,40,43,80–82]. In this sense, our perspective is that Long COVID and VSITV are mainly (although not exclusively) a form of thrombotic vasculitis.

Microclots in Long COVID patients were first described by Pretorius et al. [82], who found a persistent presence of fibrinolysis-resistant microclots in the blood, accompanied by platelet hyperactivation and dysregulated hemostasis disturbance. These microclots were visible macroscopically as a pellet in platelet-poor plasma samples after centrifugation (not seen in healthy controls or patients with type 2 diabetes), and levels were comparable to those found in patients with acute COVID-19 [82].

Clogging of the capillaries

Normally, human capillaries are 5–10 μm in diameter, allowing red blood cells (~8 μm in diameter) to circulate in single file due to their flexible structure [83]. However, microclots present in Long COVID patients have a diameter of 5 to 200 μm, which means that they can obstruct capillaries [82,83]. This can lead to ischemia- reperfusion injury at the microvascular level [83], explaining exacerbation of symptoms after physical exertion (PESE), which affects 75-89% of patients. PESE is a diagnostic criterion for myalgic encephalomyelitis, which can be objectively demonstrated by cardiopulmonary exercise tests performed on consecutive days [1,83–87], and subsequent recovery is prolonged [88].

Microvasculature obstruction also explains other symptoms of Long COVID, such as chest pain, which can be caused by microvasculature ischemia [89]. Evidence of capillary obstruction has been found in several studies of the microvasculature of different organs in patients with Long COVID, providing evidence of systemic vascular changes [89–95]. These microvascular changes include a reduction in sublingual vascular density comparable to that seen in severe cases of acute COVID-19 [93], as well as a reduction in retinal vascular density [94,95], presence of fibrin thrombi obstructing capillaries in the skin [92] and loss of muscle capillaries [90,91]. Biomarkers of tissue hypoxia-induced microvascular remodeling, such as vascular endothelial growth factor (VEGF), have been found in patients with Long COVID, probably as compensation for capillary occlusion [96-98]. However, any new vessels that form will also be susceptible to occlusion. Similar compensatory angiogenesis has been observed in multiple organs of severely acute patients with COVID-19 [99]. These findings are compatible with capillary occlusion by microclots.

Similar data have been observed in histopathology studies in patients suffering from VSITV, especially microscopic vasculitis and microthrombosis in different tissues and organs. In fact, a recent work reports the postmortem study of 325 patients who died after administration of the mRNA-based vaccines. They found that 53% of deaths due to VSITV affected the cardiovascular system, 17% the hematological system, 8% the respiratory system, and 7% affected multiple organ systems. Three or more systems were affected in 21 cases. A total of 240 deaths were directly adjudicated to vaccination with mRNA-based vaccines (103).

The presence of a coagulopathy in patients with Long COVID goes beyond “typical” symptoms and is associated with increased risk of cardiovascular disease, such as ischemic heart disease and myocardial infarction after acute COVID-19 infection [100–102]. Although this risk decreases with time, coagulopathic processes still persist in some people, suggesting that this condition is ongoing. Microclots have been found even more than 23 months after SARS-CoV-2 infection [82,103-109].

In addition, a sustained increase in circulating thrombogenic spike protein S1 subunit has been observed in Long COVID patients compared to those who have recovered from COVID-19 infection [67,110– 112], which may explain the risk continuous thrombosis in some cases. Analysis of COVID-19-induced microclots has also revealed the presence of spike protein (but not full-length SARS-CoV-2) and inflammatory markers within the clots [58,66,113]. Thus, clot dissolution can perpetuate clot formation and platelet activation by releasing trapped spike protein and inflammatory proteins, creating a vicious cycle [113,114]. Inflammatory protein retention/sequestration may also help explain why many patients with Long COVID and VSITV may present with "normal" laboratory test results. The most common test involves C-reactive proteins, which are elevated during inflammation, and may suggest blood clot formation. Pretorius’ research found that the insoluble microclots formed in long COVID tend to entrap inflammatory markers such as C-reactive proteins. Since these markers are no longer dissolved in plasma, when doctors take a sample of the plasma solution, the results return as normal. Another standard test for blood clots checks D-dimer levels. However, D-dimers are only released when blood clots begin to break down. As a result, patients who have blood clots but have not yet broken them down may frequently yield normal test results.

Platelet activation and endothelitis

Platelet hyperactivation and endothelitis are important features accompanying microclots in Long COVID and VSITV [43]. Endothelial damage markers in Long COVID correlate with increased symptom burden and decreased exercise tolerance [103,105,107,109,115–121], while hyperactivated platelets amplify and maintain endothelitis [116], contributing to the development and maintenance of Long COVID [82,104,108,122,123]. Furthermore, Long COVID patients who experience more pronounced cognitive deficits show higher levels of cerebral hypoperfusion [124] and neuroinflammation [125], with plasma inflammatory markers consistent with endothelitis [118,126,127]. Since endothelial dysfunction is a precursor to atherosclerosis, complications of COVID-19 could manifest in the coming decades [128].

Capillary occlusion caused by microclots and endothelitis

can lead to poor systemic oxygen extraction [43,129– 133]. Long COVID patients have higher blood lactate levels at rest and during exercise, indicating a lower anaerobic threshold [130]. The reduction in maximal oxygen consumption (VO2 max) in Long COVID patients is due to peripheral limitation in oxygen delivery due to poor oxygen extraction at the capillary level [130-133], rather than physical deconditioning [134]. Indeed, poor oxygen extraction has been shown to be associated with exercise intolerance in Long COVID patients, along with plasma markers indicating endothelitis [133].

These findings are radiologically supported by magnetic resonance imaging using 129 xenon, which demonstrate impaired pulmonary gas transfer in Long COVID patients, attributed to microclots, and correlated with decreased exercise tolerance and increased blood desaturation. oxygen after physical exertion [136,137]. Ventilation/perfusion scans and single photon emission computed tomography (CT) after COVID-19 are preferable for evaluating capillary thrombosis and perfusion defects, as conventional CT pulmonary angiography may underestimate these problems [138], even in pediatric cases [139,140].

Taken together, these findings support the existence of microclots and may help explain the wide variety of symptoms in Long COVID due to multiorgan tissue hypoxia [129,131–133,136].

Co-pathologies

Beyond the central problem of tissue hypoxia resulting from thrombotic vasculitis, there are other consequences of persistent endothelial inflammation. Patients with Long COVID are at significantly elevated risk (HR > 80) of dysautonomia [79], and some symptoms, such as

postural tachycardia, may be partly explained by coagulopathy, particularly early in disease progression [80]. The autonomic nervous system innervates the walls of blood vessels to regulate vascular tone [32]. Sympathetic and parasympathetic fibers innervate the muscular layer of the vessels, while only parasympathetic fibers innervate the endothelial layer, making parasympathetic fibers more susceptible to the consequences of endothelial inflammation [32]. Nerve ischemia has been proposed as an etiology [9]. The resulting dysautonomia, where sympathetic function predominates, which is in the moderate to severe range in two-thirds of Long COVID patients, is independent of the initial severity of the infection [32,141] and is associated with exercise intolerance [142].

An important consequence of post-COVID- 19 dysautonomia is postural orthostatic tachycardia syndrome (POTS) [143]. The etiology of POTS is multifactorial, but endothelial disease [144], hyperactive plat e le t s [145 ,146], tissue hypoxia [147], immunethrombosis [146], and increased sympathetic activation [144,147–149] have all been implicated. POTS causes abnormal cerebral blood flow and oxygenation [150,151] consistent with the target organ consequences of thrombotic vasculitis in Long COVID and contributes to a variety of common Long COVID symptoms (eg, fatigue, tremors, dizziness) [152]. Predominant sympathetic activation produces symptoms that can commonly be misdiagnosed as anxiety [153-155]. ACE2 downregulation and tissue hypoxia can reduce serotonin synthesis [156,157], while overactive platelets (which store serotonin) can cause serotonin depletion [113]. Therefore, the anxiety and depression present in some patients may be a consequence of coagulopathy and dysautonomia [158].

More cases of POTS have been observed after SARS- CoV-2 infection and vaccination (less frequent) [143,159]. It is increasingly recognized (see above, VSITV foundations) that Long COVID symptoms, diagnoses, and pathophysiology may also be triggered after SARS-CoV-2 vaccination in some patients [7,8,10,11] in which the persistence of the spike protein has been implicated [7–9]. With the same diseases occurring after vaccination and infection, we here suggest that the persistence of the spike protein (rather than the whole virus) may lead to Long COVID, POTS, and VSITV pathology. Given that the spike protein alone has been shown to induce microclotting in vitro [36] and that some of those vaccinated with an mRNA-based vaccine develop a thrombotic vasculitis similar to that of Long COVID-19, we believe this offers crucial insight of the etiology of Long COVID-19 and VSITV. Supporting this, and in line with the evidence presented above for Long COVID, several cases of post-COVID-19 vaccine retinal vascular occlusion (summarized in [160]) have been reported, attributed to Susac syndrome (an autoimmune endotheliopathy) and microthrombi, with potential links to hyperviscosity syndrome.

It is true that mast cell activation syndrome (MCAS) appears to play an important role in both Long COVID and postural orthostatic tachycardia syndrome (POTS). Mast cells, found in the vasculature, are involved in inflammation, hemostasis, and endothelial cell activation. Their degranulation may contribute to immunological and thrombotic outcomes in COVID-19. In turn, platelet activation and ischemia-reperfusion can stimulate mast cell degranulation. Several mast cell mediators, such as heparin, tryptase, and VEGF, are directly involved in coagulopathy.

Thus, MCAS may be a direct consequence of persistent coagulopathy, even if activation was initiated through spike protein exposure. The persistence of the spike protein may be a chronic trigger of MCAS. Although MCAS appears to be a co-pathology in some Long COVID patients, addressing the coagulopathy could have a dual benefit by reducing inappropriate and harmful mast cell activation as well as mitigating thrombogenesis.

Current evidence suggests that both Long COVID and VSITV are mostly a coagulopathy and vasculopathy causing multisystem symptoms due to systemic tissue hypoxia. The clinical similarity with other coagulopathic diseases, such as antiphospholipid syndrome, also supports this idea.

Thus, it is likely that Long COVID and VSITV are, in many cases, Spike protein-induced thrombotic vasculitis (SITV). Therefore, the use of the terms NSITV and VSITV is proposed to describe these disorders, as they are more descriptive of the proposed mechanism and primary pathology. This helps focus attention on early therapeutic interventions to prevent chronic complications and also distinguishes these conditions from other pathologies that may predominate in some patients.

Importantly, this proposal is supported by current evidence, but research on Long COVID and VSITV is ongoing, and further studies are needed to fully understand their pathophysiology and develop effective therapeutic approaches.

Potential treatments

Therapeutic efforts for Long COVID to date have focused predominantly on rehabilitation and psychological therapy [169], perhaps due to the impression that Long COVID patients are recovering from acute COVID-19 rather than suffering a continuing pathology. Taking this pathology into account, these treatments can be harmful, due to PESE [1,87,170]. In fact, rehabilitation is largely ineffective in improving Long COVID symptoms [169]. We maintain that Long COVID patients (those with NSITV) will not be ready for rehabilitation until the underlying disease and its complications have been effectively treated.

Treatment targets for NSITV and VSITV are microclots, hyperactive platelets, and endothelitis. It is proposed that treatment of this multifaceted inflammatory coagulopathy with a single drug will be insufficient and a combination of anticoagulant, steroidal anti-inflammatory, and antiplatelet drugs will be required to achieve synergistic and superior results [81,114,156], and early intervention is recommended [43,114,156].

Anticoagulants

In acute cases of COVID-19, favorable outcomes have been hypothesized and achieved when coagulopathy is addressed [38,171,172], and NICE recommends anticoagulants in certain circumstances [173]. In a case series of Long COVID patients, early treatment with apixaban 5 mg B.I.D. (with aspirin, clopidogrel, and a proton pump inhibitor) for ≥1 month resulted in symptomatic resolution in 24/24 patients [81]. Symptomatic improvement was also correlated with a reduction in microclots and hyperactive platelets. Another case series (n=91) of anticoagulant/ antiplatelet therapy showed that between 74% and 87% of patients reported an improvement in nine key symptoms and a concurrent reduction in microclots, but an increase in gastrointestinal bleeding [80].

Since Long COVID microclots are resistant to fibrinolysis [36,69,78], dabigatran may be superior, as it increases clot susceptibility to fibrinolysis more than other anticoagulants [174,175]. Heparin inhibits the binding of the ACE2 spike protein, which means that it has antiviral and anticoagulant properties [60,176–178]. Heparin has been used to effectively treat conditions such as prolonged COVID-related perfusion defects [139], as well as microclots in the setting of pulmonary embolism [179]. In addition, obstetric patients (n=291) with Long COVID who received enoxaparin antepartum through six weeks postpartum reported ongoing symptoms of Long COVID less frequently than those who did not [180].

Antiplatelet drugs

The targets of antiplatelet therapy are hyperactive platelets and endothelitis. Emerging evidence suggests a unique role for P2Y12 inhibitors (eg, ticagrelor, clopidogrel) that attenuate the interaction between platelets and endothelial cells and thus reduce platelet activation, endothelitis, and endothelial formation. clots more potently than aspirin [58,116]. In hospitalized patients with acute COVID-19, favorable outcomes (eg, reduced mortality) have been found with antiplatelet drugs, with increased survival being observed with dual antiplatelet therapy without increased risk of bleeding [181,182]. Others have found improved

perfusion with tirofiban, along with aspirin, clopidogrel, and anticoagulants in prophylactic doses [183]. In a randomized controlled trial, hospitalized patients receiving aspirin had similar 28-day mortality rates (versus standard care), but a slightly shorter hospital stay and a higher proportion of patients discharged alive within 28 days. days [184]. In Long COVID terms, obstetric patients taking aspirin 325 mg/d reported symptomatic improvement compared with those that did not [180]. In a case series of 24 Long COVID patients, aspirin was shown to reduce hyperactive platelets as a single agent, but required the addition of apixaban and clopidogrel to reduce microclots [81]. Similar findings were reported in a larger case series (n = 91), which showed reduced platelet activation after anticoagulation with dual antiplatelet agents [80]. Considering the emerging evidence of Long COVID-like vaccine reactions, we note that aspirin has previously been explored as a method to reduce vaccine-induced acute endothelitis [185].

mTORC1 Inhibitors

A drug that should be considered is Rapamycin or Everolimus, an mTORC1 inhibitor that has excellent anti- inflammatory effects on endothelial cells in addition to its immunosuppressive effect that has given very good results in Takayasu vasculitis, kidney transplant rejections, Grant versus host disease and its use in coronary stents to prevent endothelial and myocyte proliferation of the arterial medial layer. It is the author's opinion that the most reasonable treatment for severe NSITV and severe/serious VSITV, taking into account the importance of thrombotic vasculitis in its pathogenesis, is made up of: steroidal anti-inflammatory (Deflazacort doses of 15 to 30 mg / day , prednisolone 10-20 mg x day), anticoagulant (Apixaban 5-10 mg x day, Dabigatran 110-150 mg x day,), antiplatelet drugs (Clopidrogel 75 mg BID x day, Ticagrelor 60-90 mg x day) and Rapamycin 1 mg BID x day or Everolimus 10 mg x day. In cases of mild to moderate NSITV and VSITV, the use of low doses of steroidal anti-inflammatory drugs, anticoagulants, and antiplatelet drugs should be considered, and in cases in which no improvement is obtained, consider the use of Rapamycin or Everolimus.

Those patients with NSITV and VSITV with symptoms of anxiety and depression may benefit from the antidepressant Sertraline; this drug also has additional antiplatelet and endothelial protective properties (188-193). In addition, sertraline binds to the S1 subunit of the spike protein, blocking its interaction with ACE2 [187], which may be important considering the growing evidence of persistence of the spike protein in NSITV and VSITV.

Conclusion

A growing body of evidence supports that NSITV and VSITV i s primarily an endothelial and immunocoagulopathic disease initiated by SPIKE expression in cells following infection or the use of mRNA platform-based vaccines. We propose the use of the term NSITV and VSITV as it describes the pathophysiology of post-COVID-19 and post-vaccination presentations, and helps focus attention on early therapeutic intervention targeting microclots, hyperactive platelets, and endothelitis. This multifaceted coagulopathy requires synergistic polypharmacy to achieve symptomatic resolution. Thromboelastographic can be used to mitigate the risk of bleeding.

Our perspective does not deny the need to find and treat other common pathologies in Long COVID and VSITV, but highlights how thrombotic vasculitis can cause, exacerbate, and interact with other pathologies. Future research should investigate the efficacy of aggressive anticoagulation, antiplatelet therapy (particularly early), and the use of Rapamycin/Everolimus, after COVID-19 infection or post-mRNA vaccine sequelae to treat NSITV and VSITV.

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