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Mini Review

Clinical Trial to Test Safety and Efficacy of RNA-Based Immune Support in Long COVID Patients

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Abstract

The Beljanski Foundation is sponsoring a new clinical trial for patients with Long COVID because of the urgent need for a new and successful treatment. The goal is to test whether administration of a special preparation of small RNA fragments resolves symptoms in Long COVID patients. Originally developed by M. Beljanski, the fragments work by stimulating stem cells in bone marrow to produce our immune cells. Previous research conducted on this special preparation of small RNA fragments at Cancer Treatment Centers of America confirmed their safety and effectiveness for treating thrombocytopenia (low platelets) caused by chemotherapy. Thrombocytopenia, as well as immune dysregulation, have been seen in a significant number of Long COVID patients and low platelets are associated with fatigue, a major symptom of Long COVID. The trial will also reveal the potential of the RNA fragments to re-balance immunity in these patients.

Keywords: *Long Covid; COVID-19; SARS-CoV-2; Platelets; Thrombocytopenia; Clinical Trial*

Introduction

Anecdotal reports from patients experiencing lingering symptoms from an infection with SARS-CoV-2 started to emerge shortly after the beginning of the pandemic and the term "Long COVID" was coined to name this condition and alert the scientific community.

According to the Centers for Disease Control and Prevention [1], 1 in 5 people infected with the severe acute respiratory syndrome coronavirus (SARS-CoV-2) eventually experience long-term effects from their infection. Other studies indicate that the number is higher [2]. People call post-COVID conditions by many names, including Long COVID, long-haul COVID, post-acute COVID-19, post-acute sequelae of SARS-CoV-2 infection (PASC), long-term effects of COVID, and chronic COVID.

Whatever the name, according to the World Health Organization there have been over 758 million people around the world infected since the inception of the pandemic [3]. Nature Reviews estimates that upwards of 65 million people are currently suffering from Long COVID worldwide [4], and the real numbers could be higher, because – according to the Centers for Disease Control and Prevention - people who are vaccinated are less likely to report post-COVID conditions, compared to people who are unvaccinated [5].

Most patients who become infected with COVID-19 recover without complications within a few days to a few weeks after infection, so post-COVID conditions can be first identified when patients complain of a wide range of new, returning, or ongoing health problems.

In both the "National Research Action Plan on Long Covid" and the "Services and Supports for the Longer-term Impacts of Covid-19", the following interim federal working definition of "Long COVID" is presented as follows: "Long COVID is broadly defined as signs, symptoms, and conditions that continue or develop after initial COVID-19 or SARS-CoV-2 infection. The signs, symptoms, and conditions are present four weeks or more after the initial phase of infection; may be multisystemic; and may present with a relapsing-remitting pattern and progression or worsening over time, with the possibility of severe and life-threatening events even months or years after infection. Long COVID is not one condition. It represents many potentially overlapping entities, likely with different biological causes and different sets of risk factors and outcomes".

Since July 2021, "Long COVID" has become a recognized condition that could result in a disability under the Americans with Disabilities Act (ADA).

A survey of 3,762 Long COVID/PASC patients, from 56 countries found nearly half still could not work full-time 6 months post-infection, due mainly to fatigue, post-exertional malaise, and cognitive dysfunction [6].

One of the most significant differences in the gene expression in the blood of individuals at 6 months post-infection compared to those who didn't suffer Long COVID symptoms, was related to platelets, small blood cell fragments that help with clotting and tissue repair [7]. A meta-analysis of 7,613 COVID-19 patients revealed that patients with a lower platelet count tended to have more severe disease than those with a healthy platelet count. Finally, some studies, although not all [8,9], have found platelet counts to be a predictor of COVID-19 mortality.

Data suggests that Long COVID patients may have reduced platelet counts or activity known as thrombocytopenia, also called idiopathic thrombocytopenic purpura (ITP) [10].

While it appears that ITP is a common complication of COVID-19, it is also a common cause of thrombocytopenia after viral infections [11].

Viral infection can be associated with thrombocytopenia due to a variety of causes [12]. Platelets can be activated by viral antigen-antibody complexes and then cleared from the circulation by the reticuloendothelial system [13]. SARS-CoV-2 can also infect megakaryocytes as well as platelets [14], leading to the destruction of circulating platelets and megakaryocytes in the bone marrow [15].

There is a growing appreciation for the contribution of platelets to immunity, beyond the well-documented functions associated with vascular injury and the prevention of bleeding: Platelets interact directly with viruses via a variety of receptors [16] and play a role in recruiting and activating circulating leukocytes, principally neutrophils, to sites of inflammation [17]. Able to engulf and aggregate pathogens, platelets combine thrombotic and immune recruitment functions. They play an important role in inflammatory signaling as well as in infection response [18].

Whereas circulating immune complexes (ICs) contribute to both chronic and acute inflammation in a multitude of clinical conditions, recent studies reveal platelet contributions to inflammation in reactions involving ICs [19,20].

Moreover serotonin, 5-hydroxytryptamine, a hormone and a neurotransmitter mostly known for its role in mood, anxiety, psychosis, is stored in platelets [21] the remainder being located in the central nervous system, the cardiovascular system, the intestinal nervous system, and the blood. Depending on the receptor to which it binds, it has a "stabilizing" effect. Serotonin stimulates memory or promotes deep sleep. It influences most brain cells, directly and indirectly, and helps transmit information between neurons.

Platelet levels have been measured in depressed patients and have been found to be decreased when compared to normal controls. Therefore, interference in this process might be a promising avenue for further research to address mild thrombocytopenia in people with Long COVID, along with the most common side effects of this condition, which are fatigue and depression. Yet, severe bleeding events are uncommon in COVID-19 patients and rarely warrant conventional treatment [22]. Indeed, COVID-19 patients appear to have increased platelet consumption, together with a corresponding increase in platelet production. Conventional treatment of ITP is dependent on the platelet count and whether the patient is bleeding, with the goal of preventing or treating any significant bleeding [23]. In adults with a platelet count < 30 x 10^3/µl who are symptomatic or with minor mucocutaneous bleeding, the American Society of Hematology (ASH) recommends using corticosteroids as the first line. The vast majority of Long COVID patients would not be eligible for this type of therapy, and the side effects of corticosteroids makes the therapy undesirable.

The allure of a nutritional approach that relies on the intake of essential nutrients

Nucleic acids are large molecules found in all living cells. There are two forms of nucleic acids, the deoxyribonucleic acid (DNA) and ribonucleic acid (RNA).

DNA carries the genetic information for storing and transmitting and expressing the genes for cell growth and development. DNA was first discovered by Frederich Miescher in 1868, but its main function in the cell was only understood in 1952, when Hershey and Chase elucidated its role as the major basis for heredity [24].

In cells, RNA exists in a very large variety of molecules, each with its own role ranging from intermediate between DNA and proteins, to switching genes on and off [25], to composing ribosomes, structures that catalyze the formation of proteins [26].

RNA nucleotides are essential nutrients [27], needed to support gut health [28] and whose deficiency induces morphological changes [29]. Beljanski developed specific RNA fragments able to selectively promote healthy bone marrow stem cell duplication and differentiation, to help maintain normal leukocyte and platelet counts [30-32].

Understanding the various kinds of RNA(s) and their roles has involved the efforts of numerous researchers. Prominent contributors include Jean Brachet who in 1933 was able to show that DNA was found in chromosomes and that RNA was present in the cytoplasm of all cells [33]. Severo Ochoa and Arthur Kornberg were jointly awarded the 1959 Nobel Prize in Physiology or Medicine "for their discovery of the mechanisms in the biological synthesis of ribonucleic acid and deoxyribonucleic acid" [34] and M. Beljanski elucidated multiple roles of RNAs and also developed specific RNA fragments for immune support.

The critical role of RNA primers was first discovered by Okazaki [35]. These short segments of RNA act as primers for initiating synthesis of new strands of DNA. Bone marrow is where blood cells, both white and red, as well as platelets are generated.

Beljanski prepared polyribonucleotides obtained by degradation of the ribosomal ribonucleic acids extracted from a harmless bacteria *Escherichia coli* K-12 (*E. coli* K-12). *Escherichia coli* K-12 is not considered a human or animal pathogen nor to be toxicogenic. It is one of several microorganisms that are normal inhabitants of the intestines of virtually all warm-blooded mammals.

A successful approach to thrombocytopenia

Low platelet counts, a condition called thrombocytopenia, is a side effect of chemotherapy drugs that damage the bone marrow stem cells that normally produce platelets.

In 2010, Cancer Treatment Centers of America® (CTCA) completed a clinical trial on a commercial preparation of Beljanski's formula of RNA fragments (ReaLBuild®) that has been available as a dietary supplement since the 90's.

The clinical trial was conducted among cancer patients undergoing different chemotherapies. The Phase I trial showed that Beljanski's RNA fragments could prevent thrombocytopenia by inducing the production of new platelets. Patients taking the RNA fragments had their platelet levels return to normal and chemotherapy treatments were completed without dose reductions, suspensions, or platelet transfusions. The RNA fragments protected platelet levels in patients with many different types of cancer who were taking many different anti-cancer drugs. Moreover, patients did not suffer any negative side effects as a result of taking the RNA fragments. The results suggest further studies aimed at establishing the RNA fragments as a standard component in all chemotherapies that cause significant platelet loss. The clinical trial also compared the activity of RNA fragments obtained from *E coli* K12 with RNA fragments obtained from yeast and demonstrated the superior activity of the bacterial RNA compared to the yeast RNA [36].

Conclusion

RNA fragments for Long COVID

There are two objectives of this new study. First, to evaluate the effect of administration of the RNA fragments on restoring bone marrow function in Long COVID patients. Second, to determine whether changes in platelet and lymphocyte counts induced by the RNA fragments precede changes in symptoms or patient function. Patients are eligible for the trial if they present with thrombocytopenia and a cluster of COVID-19 symptoms, especially fatigue.

Using the COVID-19 Yorkshire Rehabilitation Scale (C19-YRS), researchers will assess the effect of the RNA fragments administration on the following Long COVID symptoms: breathlessness, cough/voice, swallowing/ nutrition, fatigue, continence, cognition, pain/discomfort, anxiety, depression, post-traumatic stress disorder, communication, mobility, personal care, activities of daily living, social role, perceived health status and family/carers views. The C19-YRS provides an overview of 3 outcomes: symptoms severity score, functional disability score and global health score. Additionally, several self-reported questionnaires will allow assessment of the effect of the RNA administration on fatigue, mood (depression and anxiety), sleep quality, quality of life, and pain. Actigraphy will provide an independent and objective measure of changes in patient activity levels, which are commonly depressed in the Long COVID population.

The findings of this new clinical trial will provide valuable insight into whether improving bone marrow function and patient immunity is a pathway for successful Long COVID treatment.

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