How to Control Covid-19 with a Nanobiotherapy?

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Abstract

The outbreak of emerging severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease (COVID-19) in China has been brought to global attention and declared a pandemic by the World Health Organization (WHO) on March 11, 2020. In a recent study of Nanshan Chen et al., on patients of Wuhan Jinyintan Hospital, Wuhan, China, from the 99 patients with SARSCoV-2 infection, 51% had chronic diseases and they had symptoms of fever (83%), cough (82%) shortness of breath (31%), muscle ache (11%), fatigue (9%), headache (8%), sore throat (5%), rhinorrhea (4%), chest pain (2%), diarrhea (2%), and nausea and vomiting (1%) [1, 2]. The majority of patients can recover, however, about 25% of patients will progress into severe complications including acute respiratory distress syndrome (ARDS), which may worsen rapidly into respiratory failure, need an intensive care unit (ICU) and even cause multiple organ failure [3]. Depending on the pathophysiological mechanisms supposed to be involved in the development of the various clinical forms of the disease, various types of treatment have been tested with varying degrees of success. We have developed a nanotherapy to block the entry of the virus into the host cell, to reduce its potential for replication and to regulate the immune response against the microbial aggressor [4].

Keywords: COVID-19 Inflammatory and Infectious Mechanisms – Adapted Therapies – BI (G) MED Nanotherapy

Introduction

SARS-CoV-2 is considered as a member of the viral family of β-Coronaviruses. It is an enveloped positive single-stranded RNA (ssRNA) coronavirus (Figure 1). Different kinds of viral and host factors (upper and lower panels) can also influence susceptibility to infection and disease progression. It was found that the genome sequence of SARS-CoV-2 is 96.2% identical to a bat CoV RaTG13, whereas it shares 79.5% identity to SARS-CoV. Today it is clear that SARS-CoV-2 could use angiotensin-converting enzyme 2 (ACE2), the same receptor as SARS-CoV, to infect humans [5].

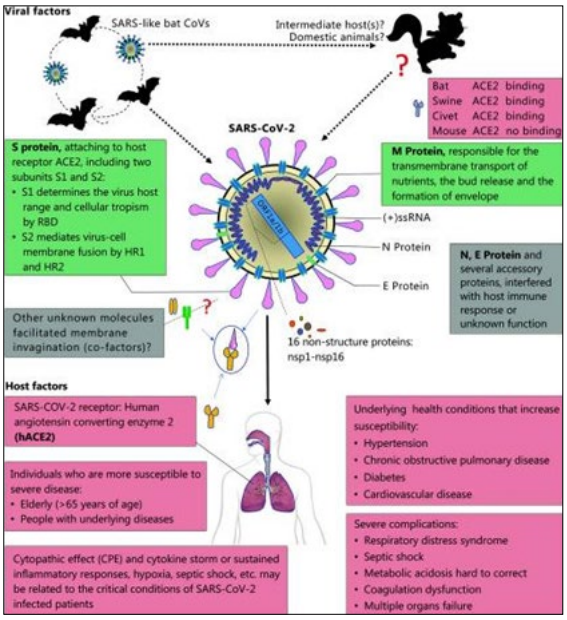

Figure 1: Yan-Rong Guo, & al, Mil Med Res. 2020; 7: 11. Viral and host factors that influence the pathogenesis of SARS-CoV-2

The genome of CoVs contains a variable number (6–11) of open reading frames (ORFs); two-thirds of the viral RNA, mainly located in the first ORF (ORF1a/b) translates two polyproteins, and encodes 16 non-structural proteins (NSP), while the remaining ORFs encode accessory and structural proteins. The rest part of virus genome encodes four essential structural proteins, including spike (S) glycoprotein, small envelope (E) protein, matrix (M) protein, and nucleocapsid (N) protein, and also several accessory proteins, that interfere with the host innate immune response. In addition, the frequency of SARS-Cov-2 mutations is, for example, much lower than that of H7N9 avian influenza.

COVID-19 Infection

Different studies have proven that host cell entry of SARS CoV-2 depends on the SARS-CoV receptor ACE2 and can be blocked by a clinically proven inhibitor of the cellular serine protease TMPRSS2, which is employed by SARS-CoV-2 for S protein priming [5].

When SARS- CoV-2 infects cells expressing the surface receptors angiotensin- converting enzyme 2 (ACE2) and TMPRSS2, the active replication and release of the virus cause the host cell to undergo pyroptosis and release damage-associated molecular patterns (DAMPs), including ATP, nucleic acids and ASC oligomers [6].

These are recognized by neighboring epithelial cells, endothelial cells and alveolar macrophages, triggering the generation of pro-inflammatory cytokines and chemokines (including IL-6, IP-10, macrophage inflammatory protein 1α (MIP1α), MIP1β and MCP1). These proteins attract monocytes, macrophages and T cells to the site of infection, promoting further inflammation (with the addition of IFNγ produced by T cells) and establishing a pro-inflammatory feedback loop (Figure 2).

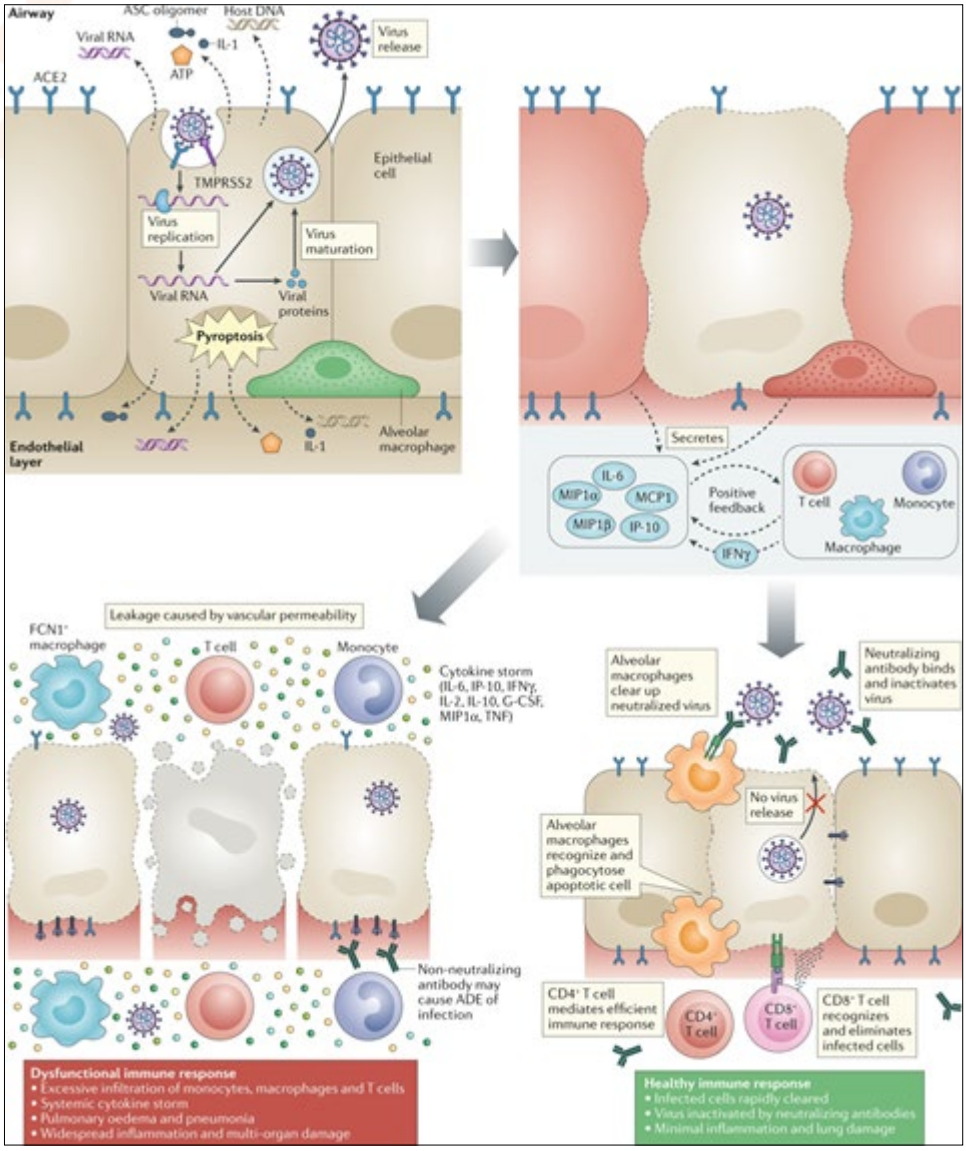

Figure 2: Yan-Rong Guo, & al, Mil Med Res. 2020; 7: 11.
Viral and host factors that influence the pathogenesis of SARS-CoV-2

In a defective immune response (left side), this may lead to further accumulation of immune cells in the lungs, causing overproduction of pro-inflammatory cytokines, which eventually damages the lung infrastructure. The resulting cytokine storm circulates to other organs, leading to multi-organ damage.

Inflammation & Coagulation

Among the target cells which will recognize these DAMPs there are therefore endothelial cells. It is well known that inflammation and coagulation constitute two host defense systems with complementary roles in eliminating invading pathogens, limiting tissue damage, and restoring homeostasis. Extensive cross talk exists between these 2 systems, whereby inflammation leads to activation of coagulation, and coagulation considerably affects inflammatory activity. Infection leads to the production of proinflammatory cytokines that, in turn, stimulate the production of tissue factor. Pro-inflammatory cytokines and other mediators are capable of activating the coagulation system and down-regulating important physiologic anticoagulant pathways [7]. Coagulation is activated by the inflammatory response through several procoagulant pathways. Pathogen-associated molecular mechanisms (PAMPs) are also important aspects of the complex interactions between the immune response and coagulation and in sepsis [8].

At the end, it seems more and more obvious that an endothelialopathy appears to contribute to the pathophysiology of microcirculatory changes in SARS-CoV-2 infections. Emerging evidence shows that severe coronavirus disease 2019 (COVID-19) can be complicated with coagulopathy, namely disseminated intravascular coagulation, which has a rather prothrombotic character with high risk of venous thromboembolism [9, 10].

It thus appears that most patients with a severe form of COVID-19 are subjected to a cytokine storm, a particularly deleterious consequence of which is represented by major coagulation disorders, the pathogenesis of which requires further works to determine the etiological mechanisms [11, 12]. In this regard, there has been talk of a form of genetic predisposition in some patients, who would therefore be more likely to develop coagulation disorders as part of an inflammatory response to microbial attack. But if a genetic background seems obvious to the host, what about the immune system itself?

In a huge majority of cases, the meeting with SARS-Cov-2 was somehow a first for human immunocompetent cells. Never before have they been confronted with a coronavirus initially dedicated to the animal world. There was therefore no molecular mark, no cellular memory against this virus. The system was therefore obliged to compose, to do the best and very quickly and thereby triggered the strongest response possible to confront this unknown enemy. This explains the large number of extreme inflammatory reactions at the origin of the most severe clinical pictures.

The identification of the main characteristics of the SARS-Cov-2 infection leads to the implementation of a treatment involving the virus and the immune dysfunctions it induces, paying particular attention to excessive inflammatory reactions and coagulation disorders. On the basis of these pathophysiological considerations, there are therefore several therapeutic options, which ideally should be combined in a convergent approach [13, 14]. It is being understood that the ideal treatment obviously remains the primary care, which consists in preventing the virus at first sight from infecting a human being. We will consider these different approaches within the framework of a therapeutic method developed over a dozen years and called Bio Immune (G)ene Medicine, abbreviated BI(G)MED.

Materials and Methods

There are currently no vaccine or specific anti-viral drug administered to critically ill patients. The handling of such patients focuses mainly on the provision of supportive care, e.g., oxygenation, ventilation, and fluid management. Combination treatment of low-dose systematic corticosteroids and anti-virals (in some cases antibiotics) accompanied by atomized interferon inhalation have been encouraged as part of critical COVID-19 handling. Other reported therapeutic agents that are used for the treatment of seriously ill patients have been noted in Table 1 [15].

Classes	Potential treatment options
Anti-viral	>85% of patients received anti-viral agents, including oseltamivir (75 mg every 12 h orally), ganciclovir (0.25 g every 12 h intravenously), and lopinavir/ritonavir tablets (400/100 mg twice daily). Remdesivir is currently under trials at more than ten medical institutions in Wuhan and has been known to prevent MERS-CoV.
Anti-malarial	An old anti-malarial, chloroquine phosphate, has been effective in inhibiting the exacerbation of pneumonia due to its anti-viral and anti-inflammatory activities.
Herbal treatments	There was widespread use of Traditional Chinese Medicine during the last SARS-COV outbreak and it is currently being used in China. The five most commonly used herbs were Astragali Radix (Huangqi), Glycyrrhizae Radix Et Rhizoma (Gancao), Saposhnikoviae Radix (Fangfeng), Atractylodis Macrocephalae Rhizoma (Baizhu), and Lonicerae Japonicae Flo.

Table 1: Potential treatment options of COVID-19, A C Cunningham & al, Crit Care. 2020

Other therapeutic trials have involved IL-6 antagonists as well as Jak pathway inhibitors [16]. Furthermore, currently

available tests make it possible to select plasma donors with high titers of neutralizing antibodies for plasma therapy and the preparation of hyperimmune intravenous immunoglobulins. Efforts are underway to harmonize the protocols [17]. Unfortunately, most of these treatments are not harmless and can cause significant side effects. Most of these treatments allow partial improvements in clinical status, but none of them covers the disease in its full extent. This is the reason why we have sought to develop a therapy that is both global and devoid of any undesirable side effects. To do this we turned to nanobiotechnologies allowing the use of many molecules at ultra-low doses.

The product thus obtained was then dynamized by a molecular agitation technique falling under the ab initio dynamics related to quantum mechanics, which gave it a new physico-chemical stability without modifying its structure. From there, it became possible to use the principle of Hormesis well known in toxicology and aging to adapt the concentration of each molecule according to the importance of its role played during the infectious state of the disease. Hormesis is usually defined as a response of (over) compensation to an inhibiting or stimulating signal in the opposite direction [18]. Both types of effects are recognized as coming from a homeostatic overcompensation response, which optimizes an organism's capacity to take up challenges beyond the limits of its normal adaptation. Therefore, hormesis is a manifestation of two non-mutational evolutionary principles — homeostasis and optimization.

It is therefore a question of optimizing cellular functions at the level of their molecular mechanisms to restore a homeostatic state imbalanced by the viral aggression of SARS-Cov-2. For this purpose, we will apply the well-known Arndt-Schultz Law in pharmacology **(Figure 3)**, although often ignored, that underlines the reversal of action of an active ingredient in proportion with the dose used.

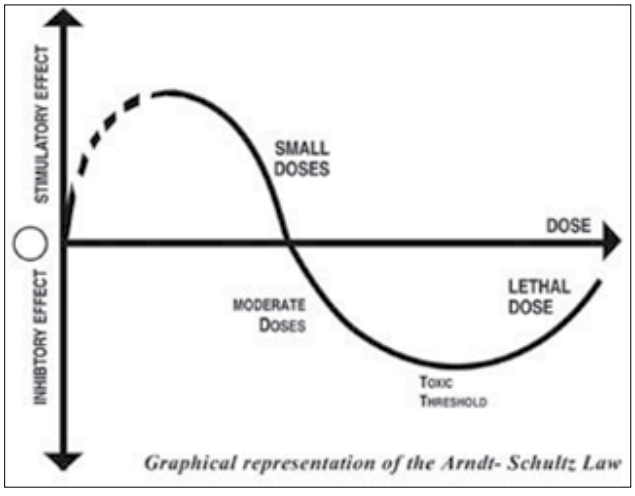

Figure 3: Graphical representation of the Arndt-Schultz Law

Applied to ultra-low doses, this law specifies that low dilutions have an activating effect whereas high dilutions exert an inhibiting effect. We therefore applied these rules and principles in the development of both "viral regulation" (viral on large spectrum) and "SARS-Cov-2 regulation" (SARS-Cov-2 on targeted scale). Hence, we called the two developed formulas VIRUSREG and COROVIR/REG. All our formulas are built according to a more or less identical general scheme combining regulation on the one hand at the epigenetic level thanks to the use of non-coding microRNAs, on the other hand at the level of the main signaling pathways involved in cellular homeostatic dysfunction responsible for the pathogenesis of the disease.

Depending on whether the objective is to activate or on the contrary, to slow down molecular expression we will use a variety of concentrations / dilutions on a scale ranging from 10×10^{-4} Mol to 10×10^{-15} Mol, which allows in most cases a very fine regulation of molecular dysfunctions. Whatever the type of disease, we favor in the formulation of the remedy the regulatory effects on the molecular level exerting a positive or negative regulatory effect on the main effectors of the signaling pathways without neglecting a direct modulation effect at these last. In the end, this way of proceeding allows to obtain a global regulation from the gene to the cell, the only one able to reinstate the initial homeostasis.

In the VIRUSREG formula, the microRNAs and the molecules of the interferon signaling pathways are thus modulated in order to stimulate in a much-framed way the appropriate anti-viral response. The COROVIR/REG formula is a little different in its conception since studies on the epigenetics of SARS-Cov-2 are currently non-existent. Consequently, the objective was on one side to lock the entry doors at the level of the ACE2 and TMPRSS2 receptors and on the other side, to inhibit the potential for replication of the SARS-Cov-2 virus by blocking the expression of the RNA responsible for this one.

Results

Unfortunately, we do not have any sponsorship likely to allow us to implement a large-scale study of our treatment within the frame of a rigorous methodology; we simply follow up patients in the context of consultations in city medicine. For the past three months, many patients in various European countries have benefited from this treatment, which has enabled them in the vast majority of cases to be spared from the pandemic or, in a minority of cases, to develop a very attenuated form of the disease by avoiding progression to a more severe phase.

Conclusions

The aim of this work was to make the scientific community attentive to a new type of treatment using nanodoses of various types of molecules involved in the deregulation of cell homeostasis triggered by the intrusion of SARS-Cov-2. It is important to emphasize that it is an empirical approach by a biomimetic treatment devoid of any side effect by the means the remedies are prepared. However, our clinical observations allow us to emphasize the remarkable impact in terms of

effective prevention and extremely low morbidity. This is why we hope that the BI(G)MED therapy will arouse the interest of certain institutes or foundations ready to step in as sponsors to support our research and allow the BI(G)MED clinical therapeutic approach to progress.

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