Towards a more effective strategy for COVID-19 prevention (Review)

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Abstract. At the end of 2019, a new disease, similar to severe acute respiratory syndrome (SARS) associated with SARS-CoV was reported in Wuhan, China. It was quickly discovered that the etiological factor of the new disease (COVID-19) was a previously unknown SARS coronavirus 2 (SARS-CoV-2). The global spread of COVID-19 has lead to the declaration of a pandemic status in 2019-2020 as declared by the World Health Organization and Public Health Emergency of International Concern. SARS-CoV-2 characterizes with high epidemic potential and is effectively disseminated between humans. SARS-CoV and SARS-CoV-2 are closely related pathogens. Their prime route of distribution is air-droplet transmission. Combating infectious diseases disseminated by inhalation is very difficult, and mainly relies on the use of vaccines. However, despite the lack of an effective anti-SARS-CoV vaccine and specific antiviral drugs, the strict sanitary procedures proved to be sufficient to stop the SARS epidemic in June 2003. However, epidemic research has indicated that SARS-CoV-2 is transmitted in humans significantly more effectively than SARS-CoV; therefore, the COVID-19 pandemic continues to expand. This indicates that the so far anti-epidemic activities to control COVID-19 are insufficient. In the current review, the possibility of using interferon α (IFN-α) as a preventive agent of COVID-19 is discussed. The current data concerning anti-COVID-19 vaccines and specific drugs against SARS-CoV-2 are also discussed. The aim of the current review is to contribute to the introduction of a more efficient strategy in the protection of the human population against COVID-19.

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1. Introduction

SARS-CoV-2 is characterized with high epidemic potential. Since the beginning of 2020 it has been quickly transmitting among people in the world, usually causing an acute respiratory disease of the respiratory system - COVID-19 (1). The occurrence of the new disease, resembling severe acute respiratory syndrome (SARS) was identified at the end of 2019 in Wuhan, China (2-4). The incubation period of the disease is 2-14 days, usually 3-7 days. The earliest common symptoms of COVID-19 are fever, cough and dyspnea (5). Recently presented meta-analysis report their occurrence as follows: 87.3, 58.1 and 38.3%, respectively (6). It is noted that the typical clinical features are interstitial pneumonia (75.7%) and ground glass opacification (69.9%) in chest X-ray (5). The manifestations of the disease often include the symptoms from the gastrointestinal tract, like diarrhea, nausea/vomiting and abdominal pain. Meta-analysis reported occurrence of these symptoms as follows: 9, 6 and 4%, respectively (7). In severe cases COVID-19 may cause progressive pneumonia, acute respiratory distress syndrome (ARDS), multiple organ failure, and death. In the result of rapidly spreading SARS-CoV-2, until March 13, 2020, infections with the new coronavirus were reported in the total of 138 countries on all continents (except for Antarctica), with over 145 thousand reported infections including over 5 thousand deaths (8). Due to the global outbreak of COVID-19 the pandemic status 2019-2020 was declared by the World Health Organization (WHO) and the Public Health Emergency of International Concern (PHEIC) on March 11, 2020 (9,10). Whereas, much earlier strict sanitary procedures, including isolation of the sick and mandatory quarantine for exposed persons (contacts) were introduced. Despite the anti-epidemic proceedings, the global count of COVID-19 patients has been increasing, and according to Center for Systems Science and Engineering (CSSE), exceeded...
26 million people, including over 864 thousand deaths (as at September 3, 2020) (11). It is estimated that approximately 10% of global population may have been infected. The prime way of SARS-CoV-2 dissemination among humans, similarly to SARS-CoV, is air-droplet transmission (contagiousness of both viruses survives in the air up to 3 h). Moreover, the viruses can be transmitted through direct contact with infected persons or indirectly via coronavirus contaminated materials/objects (12,13). SARS-CoV and SARS-CoV-2 are closely related pathogens. They demonstrate around 80% homology in genomic sequence of nucleotides and they share highly conserved receptor binding domain for their S proteins (14,15). Those viruses caused acute infection in humans through the same target receptors: angiotensin-converting enzyme 2 (ACE2) together with transmembrane serine protease 2 (TMPRSS2) (16,17). It is commonly known that controlling infectious diseases disseminated by respiratory ways is very difficult, and mainly relies on the use of vaccines. However, despite the lack of an effective anti-SARS-CoV vaccine and antiviral drugs, strict sanitary procedures proved to be sufficient to stop SARS epidemic occurring from November 2002 till June 2003 in China, and subsequently in 36 other countries of the world (on 3 continents in total) (18-20). On the other hand, epidemic research show that SARS-CoV-2 is transmitted in humans more effectively than SARS-CoV, the transmission of SARS-CoV-2 may occur prior to symptomatic disease (21-23). In the light of such data it may be concluded that the anti-epidemic activities aiming at combating COVID-19 are insufficient and require new approach to preventing this disease in high-risk populations.

2. Anti-COVID-19 vaccine

Quick progress of works on anti-COVID-19 vaccine allows expecting its availability for large-scale distribution by the end of 2020. According to WHO data, 28 candidates vaccines are currently in clinical evaluation, and for 8 of them phase 3 tests are pending (24). The last group contains traditional preparations containing whole-inactivated virus, and genetic, including recombinant adenovirus type 5 vector, encoding single S-protein of SARS-CoV-2 (25). It is suspected that vaccine candidates involve the full-length S protein which may induce both neutralizing and non-neutralizing (with the wrong specificity) antibodies. The vaccine should induce long-lasting active acquired immunity (humoral and cellular) against a specific pathogen, effectively preventing the development of a disease caused by that pathogen (26-28). Vaccines containing inactivated viruses or nucleic acids encoding a specific viral protein may induce high level of specific IgM and IgG in blood. However, they usually do not stimulate cellular immunity related to cytotoxic T lymphocytes (CTL) which effectively prevent viral infection spreading. In the consequence of use of the vaccine, it is finally expected that an immune population barrier against the specific infections disease will develop, and in the result will eradicate it. Considering the data presented above, it seems that the effectiveness of none of the above preparations will be satisfactory.

The basic condition of a common use of a vaccine in healthy people is safety. At present, there is a risk that vaccination could make subsequent SARS-CoV-2 infection more severe (29-31). There are two different antibody-mediated syndromes. One is antibody-dependent enhancement (ADE) of infection and the other is vaccine-associated enhanced respiratory disease (VAERD). ADE phenomenon conditions the presence of non-neutralizing or sub-neutralizing antibodies, which bind to the virus particles. Virus-antibody immune complexes are internalized into host cells via interaction of the antibody Fc region with the cellular Fc receptors (30,32). So, in ADE mechanism the target cells are myeloid lineage cells with Fc receptors expression. In contrast, SARS-CoV-2 primarily infects pulmonary, endothelial, renal, and intestinal parenchymal cells that express ACE2. Therefore, Fc receptor mediated ADE not only intensifies the infection of already susceptible cells but also can expand tropism to, e.g., monocytes and macrophages. Moreover, internalized immune complexes can cause suppression of the cellular innate antiviral response (32). In the consequence, this leads to the enhancement of viral replication and exacerbation of clinical symptoms. In some patients with COVID-19, approximately 7th to 14th day of illness a dramatic decline in respiratory function occurs. It is suggested that the pathomechanism of this phenomenon is similar to Fc receptor-mediated ADE, the formation of immune complexes may activate monocytes/macrophages to trigger a cytokine storm (32-34). The above data, and the earlier in vitro tests with the use of serum from SARS-CoV patients with S protein-specific antibodies indicate that the therapeutic use of convalescents’ plasma with anti-SARS-CoV-2 antibodies could facilitate infecting monocytes/macrophages and in the consequence cause disease exacerbation (35,36). ADE has been described after immunizing cats with a vaccine against veterinary coronavirus (37,38).

VAERD is a distinct clinical syndrome, it mainly occurs after the use of a vaccine containing conformationally incorrect antigens. VAERD may be the result of two major mechanisms of immunological phenomenon, which are associated with enhanced respiratory disease (30,32). One of them is conditional upon immune complex formation and complement deposition in lungs tissue (in the presence of high viral load). Whereas the other is associated with complement activation, expression of proallergic cytokines and in the result, with the development of allergic inflammation (39). VAERD was demonstrated in humans immunized with vaccines for measles and respiratory syncytial virus (RSV) and in animals for SARS (40-42).

3. Anti-SARS-CoV-2 drugs

According to WHO (43), Centers for Disease Control and Prevention (CDC) (44), and the US Food and Drug Administration (FDA) (45), there is still no antiviral drug that could be useful in the prevention or therapy patients with early symptoms of COVID-19. Currently, 12 drugs are in clinical trials against COVID-19, registered by the WHO (46). Three drugs are in advanced clinical trials: remdesivir, chloroquine and hydroxychloroquine, granted with FDA emergency authorization for treatment of hospitalized patients with severe COVID-19 (47,48). On the other hand, the China International Exchange and Promotive Association for Medical and Health Care (CPAM) recommended, only in clinical trial, the use of lopinavir-ritonavir in hospitalized older patients.
with severe COVID-19 (49). Remdesivir is a novel, relatively safe compound, being a phosphoramidate, and constituting a prodrug. This compound is metabolized into its active form, and adenine nucleotide analogue that interferes with viral RNA - dependent RNA polymerase (RdRp) leading to inhibition of RNA synthesis. In vitro tests, as well as in animal experiments show that remdesivir may effectively inhibit SARS-CoV-2 infection in humans (50,51). However, it is still uncertain whether remdesivir causes direct antiviral effect on the enhanced clearing of viral loads in the respiratory tract. Whereas chloroquine and hydroxychloroquine are drugs with many years’ history of clinical use for the prophylaxis and treatment of malaria, and for the treatment of chronic Q fever and various autoimmune diseases (52). In comparison to chloroquine, hydroxychloroquine is less toxic while it demonstrates similar activity. Those drugs demonstrate antiviral activity by interfering with glycosylation of ACE2 receptor and elevating the pH in endosomes. Both medicines can inhibit the SARS-CoV-2 cell entry (53-55). The presented clinical trials confirmed that the use of those drugs promote laboratory virus - negative conversion and shortening the course of COVID-19. However, certain adverse effects in patients treated for COVID-19 were described, such as retinopathy, neuromyopathy, nephromyopathy, and cardiomyopathy due to chloroquine/ hydroxychloroquine (48,53). Whereas, lopinavir-ritonavir is a combination antiviral drug actively inhibiting viral protease, the enzyme that is essential for maturation in viral replication. Lopinavir-ritonavir is used for treatment of HIV-infected individuals, as it is characterized by high specificity for HIV protease (56). The activity of the drug, expressed through e.g. the reduction of viral load was also confirmed in patients infected with SARS-CoV (57). However, the randomized, controlled trial in adults hospitalized with severe COVID-19 has proven that lopinavir-ritonavir did not significantly accelerate clinical improvement, and did not reduce the viral load. On the other hand, gastrointestinal adverse events including nausea, vomiting, and diarrhea were more common consequences of lopinavir-ritonavir treatment (58).

Despite the undoubtful progress of research, the treatment of patients with SARS-CoV-2 infection is still mainly symptomatic.

4. Interferon (IFN)

Until now, there are no antiviral drugs or vaccine that have been claimed to be useful in the prevention or treatment of this disease. SARS-CoV-2 infection still poses a serious threat to the health and life of people all over the world. Therefore, it is necessary to implement a new anti-COVID-19 prevention strategy based on the induction of cellular antiviral activities. It is well known that SARS infection course may be symptoms free or mild/moderate. The percentage of such cases in children aged between 2-13 years is over 90% (21). Human population is naive to SARS-CoV-2. The lack of clinical symptoms of the disease or their minimization seems to be determined by the innate immunity activity restricting the development of viral infection and its pathogenicity. However, that activity does not completely ablate viral replication, SARS-CoV-2 is able to replicate to low, detectable levels, which would explain that such patients tested positive (34,59).

In non-specific antiviral host defense the basic role is played by cellular IFN response. There are 3 types of IFN, whereas type I interferons (1 IFN) including IFN-α (13 subtypes in humans) and singular IFN-β have broad spectrum of antiviral activities (60,61). IFN-α and IFN-β are produced by almost all cells in response to viral infection. IFN α/β activity is expressed ultimately with an induction of a number of interferon-stimulated genes (ISGs) which encoded for a variety antiviral effectors (62). However, ex vivo tests showed that SARS-CoV-2 does not induce significant expression of any IFN in the infected human lung tissues (63). So, the development of productive SARS-CoV-2 infection may be a result of ineffective host IFN response. This conclusion is confirmed by tests in cultured cells, demonstrating strong reduction of SARS-CoV-2 replication IFN-α and IFN-β treatment at concentrations that are clinically achievable in patients (64,65). The results prove SARS-CoV-2 sensibility to I IFN. In addition, high level of SARS-CoV-2 replication suppression may suggest that this virus, contrary to SARS-CoV, does not show the ability to modulate IFN activity in cells. IFN-α also induces innate autophagic response via autophagosome - lysosome fusion which probably inhibits SARS-CoV-2 (66). So, the above data indicate that I IFN enhances innate immunity to SARS-CoV-2 which helps to limit virus infection/dissemination. Its induction may be of special significance during COVID-19 incubation period. Therefore, the target is to urgently consider the use of I IFN in prophylaxis against COVID-19 in adult patients with high risk of SARS-CoV-2 infection, especially those who start quarantine isolation. In much earlier clinical, randomized, controlled trials on adults there was proven the possibility to use human IFN-α-recombinant (rIFN-α, nasal spray) or natural (nIFN-α, oral lozenges) in prophylaxis against acute respiratory illness-ARI (67,68). However, considerable limitation of ARI incidents was only confirmed in patients applying rIFN-α in nasal spray only. Currently, rIFN-α in aerosolized inhalation (novoferon) is subject to clinical trials. The results obtained so far indicate that this drug (applied twice a day for 15 min for 10 days) may be both effective and safe in COVID-19 prevention (69).

The recent research also document the inhibitory activity in vitro of type 3 IFN (IFN λ), especially to the replication of SARS-CoV-2 (70). However, this effect was dependent on the type of cell line used for experiments which requires further experimental works.

5. Conclusion

SARS-CoV-2 still demonstrates very high epidemic potential. The sanitary procedures applied are not sufficient to fight COVID-19. The effectiveness of the expected anti-COVID-19 vaccine may be unsatisfactory. Until now, it has been unclear which drug would be useful in the prevention or therapy of patients with early symptoms of COVID-19. Therefore it is justified to urgently consider the use of IFN-α (in aerosolized inhalation) in patients with high risk of SARS-CoV-2 starting the mandatory quarantine.

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AS-K wrote the manuscript. AS revised the manuscript. Both authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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