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Review Article

Ahead of a vaccine: A safe method of protection against COVID-19 exists

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Abstract

In the case of current COVID-19, successful prophylactic approaches are likely to have a greater impact than successful treatment approaches. In this article, we discuss the challenges before the creation of anti-SARS-CoV-2 vaccines and opportunities of other means that can enhance non-specific immunity focusing on interferon in particular. Since efficacy of intranasal interferons against a number of pathogens throughout a period of 37 years and against COVID-19 as well as safety have been shown, this method of protection can be introduced in a short period while using a permitted off-label application approach.

Keywords

COVID-19, innate immunity, interferon, SARS-CoV-2

Introduction

Throughout the history of mankind, there have been many epidemics and pandemics claimed millions of lives. Throughout centuries, infections such as anthrax, plague, syphilis, and smallpox have taken many lives until new defenses were created in the 19th and 20th centuries. The first method of specific defense was developed by Edward Jenner. It was a

method of smallpox vaccination that eventually helped to eradicate smallpox. The vaccination approach has been the major defense method for humans throughout the 20th century. Nowadays, vaccines against a variety of infections save 2.5 million lives annually, which is more than any currently existing therapeutic methods (World Health Organization 2019). Effective vaccines can provide long-term protection against a number of viral infections (poliomyelitis, smallpox, measles, mumps, rubella, etc.) Since 1924, in the United States, vaccines have prevented an estimated 40 million cases of diphtheria, 35 million cases of measles, and a total of 103 million cases of childhood diseases (Rappuoli et al. 2014).

In addition to the infections with high fatality rate (CFR), influenza has been another challenge to human being. One such pandemic called the “Spanish flu” for example, occurred from 1918 to 1920 and primarily affected Europe and the United States, killing 20 million people officially or as it is now claimed even 40 to 50 million people thus reaching a mortality rate of 50% (Kuszewski and Brydak 2000). Milder epidemics of influenza have been taking place in different parts of the world, still killing many thousand people each year.

Seasonal flu vaccine has been widely given to the public but the efficacy is low (<50%). The problem with creating such a vaccine is due to the fact that new strains or mutated versions of known strains are emerging every year. Nowadays, new version vaccines are proposed and used, the virus still kills about 290,000 to 690,000 people annually. Therefore, almost a century after one of the most dramatic pandemics in human history, we still are not fully protected from this infection (Graham-Rowe 2011, World Health Organization 2017). Despite the advances in virology and immunology, vaccines created against influenza virus, according to the epidemiological data, have not resulted in any significant success. For example, some research shows that the maximal defense achievable by vaccination is 4.5%, while some other studies including epidemiological data show no effects on survival (Fireman et al. 2009, Simonsen et al. 2005).

In efforts to develop a new vaccine against COVID-19, the situation with the influenza virus should be taken into account in order to minimize possible unsuccessful results.

Challenges faced in the creation of anti-SARS-CoV-2 vaccines

Based on the lessons from influenza vaccine development, it should be kept in mind that designing a vaccine against viral infections in time restraint conditions is a challenging goal. In the case of SARS-CoV-2, there are a number of virus peculiarities that most likely indicate that the creation of an effective vaccine in a short period of time is challenging and a difficult-to-achieve task.

First, similar to influenza virus, SARS-CoV-2 is also prone to mutations, and Koyama et al. (2020) showed in their study that antigenic drift (the main problem with influenza virus genotype and phenotype instability) is also very likely to occur in the case of SARS-CoV-2. What is important is that among SARS-CoV-2 antigenic drift variants, 23403A>G variant

(p.D614G) is present, which means that the spike protein, the main target of B-cells, is prone to such changes. As well, a number of mutations in other non-structural proteins were observed since the virus has been studied, demonstrating the instability of this virus (Abdullahi et al. 2020).

Secondly, the past experience with unsuccessful development of anti-SARS-CoV vaccine indicates that in the case of coronaviruses, a specific vaccination approach does not work due to a number of factors. The vaccines that were shown to be effective in terms of protection were shown to be unsafe (Weingartl et al. 2004, Tseng et al. 2012). It was shown in mice that the effect of the vaccine differs depending on age. Young mice immunized with anti-SARS vaccine appeared to be protected but aged mice infected with SARS after immunization were reported to demonstrate enhanced immunopathology with eosinophilic infiltrates (Deming et al. 2006). This differential effect deserves serious attention since the aged human population is considered as a high risk group for COVID-19 infection, complications and mortality.

Thirdly, although no SARS-CoV-2 vaccine variants have been officially registered yet, the Russian vaccine Gam-COVID-Vac was approved to be used in Russia because it was shown to be safe in the first trials (Mahase 2020). However, the vaccine is very questionable not only because no large clinical trials were conducted but also because of the contraindications of the vaccine. The contraindications include acute infectious and noninfectious diseases and a number of chronic noncommunicable diseases (metabolic syndrome, chronic obstructive pulmonary disease, cardiovascular diseases, diabetes, allergy, central nervous system diseases, epilepsy, autoimmune and chronic lung diseases) (Ministry of Health of the Russian Federation 2020). This enumeration is composed of exactly the group of people who are the most vulnerable to the infection and require special protection (Chang et al. 2020). Moreover, it was shown that chronic inflammation is the major risk of death from COVID-19 (Tskhay et al. 2020). It means that the most vulnerable population is left unprotected while young and healthy people, who would otherwise most likely have a mild case of the disease thus forming herd immunity, will be vaccinated.

Another major issue related to safety is the phenomenon of antibody-dependent enhancement (ADE) or vaccine-induced enhancement that represents a problem for creation of vaccines against such viral infections as dengue virus and Ebola virus. This characteristic of coronavirus infection was reported both in vitro and for animals. Induction of sera with SARS-CoV spike protein facilitates the entry of the virus into Fc receptor-expressing cells (Kam et al. 2007). In the case of SARS-CoV, it was shown that anti-Spike protein antibodies were responsible for the infection of immune cells (Tetro 2020). Immunization of cats with feline coronavirus spike protein makes infection more complicated or even leads to death caused by enhanced infection following immunization, as it was reported in several studies (Hohdatsu et al. 1998, Vennema et al. 1990). ADE of SARS-CoV-2 is indirectly confirmed by the fact that the severity of the infection was higher among Chinese patients compared to patients from other countries who were not previously exposed to SARS-CoV. This appears to be due to the antibodies to the latter circulating in the blood of some Chinese patients (Tetro 2020). Moreover, the comparison

of several spike proteins of SARS-CoV and SARS-CoV-2 shows a high degree of similarity and in some cases were even identical (Tetro 2020). These factors demonstrate that there is a high probability of ADE in the case of COVID-19, meaning that the traditional approach to vaccine creation will not solve the problem and in some groups of people receiving such vaccines may even result in worsening the course of infection.

Long-term specific protection is also questionable since it was shown already that anti-SARS-CoV-2 antibodies do not circulate in the blood longer than about one year, reducing by half every 73 days after a mild infection (Ibarrondo et al. 2020).

Even if at some point it will be possible to resolve all of these outstanding obstacles, our current hope to have a highly effective vaccine in a short while would not be met. Based on this, it becomes obvious that an alternative approach to population protection should at least be discussed with rational consideration of adaptive immunity-based defense limitations in the case of SARS-CoV-2.

The current pandemic caused by the virus SARS-CoV-2 is significantly different from all previous epidemics in many ways including the scope of the epidemic, speed of spread, and most importantly, the seriousness of contradictions among the specialists about the measures of prophylaxis and treatment of this infection.

Unfortunately, this issue will worsen if our expectations about containment of this pandemic will not come true. The approaching season presents additional factors in the form of a large number of other respiratory infections including influenza, that will worsen the situation as well.

It cannot be claimed that a vaccine is effective until all answers to important questions, including the following, are obtained:

1. "*What is the level of the cellular and humoral immunity of the population*?" - This is essential as it predetermines the efficacy of the protection, the duration of the protection, as well as the scenario of the immune response. This in turn, will give an understanding about a necessity of primary vaccination and regularity of the boosting shots. Current experience shows that in the great majority of cases, non-live vaccines require booster shots 2 to 4 weeks after the primary vaccination.
2. "*Taking into account the difference of the immune response in different age groups, what is the efficacy of protection against this infection in high-risk groups*?" High-risk groups include aged people, oncological patients and patients with other chronic diseases, as well as obese people, and others.
3. "*How will the problem of antibody-dependent enhancement be solved*?"- Antibody-dependent enhancement may lead to the situation that susceptible people will be unprotected and the probability of their death will even be increased in the case of infection.
4. "*How rapidly is the virus changing*?"- High rate of mutations and antigenic drift could make vaccine variants unreliable in a short period of time.

Based on this, it should be realized that the speed of vaccine development is not the only answer to the challenges this pandemic creates. Development of any vaccine is a long, very painstaking process of work, followed by safety and efficacy trials. And most importantly, these trials should be conducted with all groups of future recipients.

Innate immunity vs. acquired immunity

Successful prophylactic approaches are likely to have a greater impact than successful treatment approaches for three reasons. First, successful prophylaxis means either no illness or no high mortality, whereas with successful treatment there could still be a period of illness of high severity resulting in loss of human lives. Second, prophylaxis could require less labor and be less resource-intensive than treatment and could have a higher probability of success. Third, if the viral agent is causing a contagious disease, successful prophylaxis will contain an epidemic much quicker and more effectively than therapeutic means and regimens. If the focus is on the approaches effective against a broad spectrum of viral agents, it could eliminate the limitations of specificity that existing therapeutics and vaccines have. Such approaches can be used as pre-exposure prophylaxis even when the viral agent is new or can be used for post-exposure prophylaxis (Alibek and Lobanova 2006).

This prophylactic approach can be based on a known ability of some branches of the immune system to fight any viral or bacterial agents. It is known that the immune system is composed of many different networks of cellular and soluble components that interact to eliminate pathogens. The immune system is conventionally divided into at least two distinguishable subsystems that predetermine two different types of immune responses: nonspecific (innate) and specific (acquired). Against biological agents, the first line of defense is nonspecific immunity, which is usually followed by acquired immune responses. Innate immunity responds quite rapidly and does not require a previous “memory” of a pathogen to attack and eliminate it.

Acquired immunity becomes activated following the innate immunity response and produces specific antibodies and specific cellular immunity. However, the innate immunity is considered as an effective and robust defense against viral infections, and the reaction of the innate immune system to a pathogen often predetermines the outcome of a disease. Dendritic cells, macrophages, and natural killer cells are the first cellular components of the innate immune system responsible for the antiviral response.

Interferon (IFN), an essential agent of the innate immune system, was discovered in 1957 and the name “interferon” originates from the word “interference” revealing the mechanism of its action via blockage of viral particles. Interferon is a protein produced by the immune cells related to the system of non-specific or so-called innate immunity. The body produces it as a response to any viral infection. It is capable of blocking infection development and to suppress the start and progression of apparent clinical manifestation of infection until the specific immunity mechanism starts producing factors capable of eliminating a virus. Such

factors include, for example, specific antibodies to a virus, i.e. what many companies try to create in a form of vaccine in their laboratories (Borden et al. 2007).

Interferon discovery more than 60 years ago led to the intensive development of this research field. Initially, interferons derived from human blood were produced (the derivation was done by induction of the production by the immune cells using a virus). Over time, with the development of molecular biology and genetic engineering, recombinant forms of interferons were created, and the most well studied today are interferon-alpha 2a and interferon-alpha 2b (type I IFNs). By the end of the 1970's, the first trials had begun. First, leucocyte and later, recombinant forms were tested as prophylactic means against respiratory as well as gastrointestinal viral infections (Borden et al. 2007).

Type I IFNs regulate a number of essential processes host of antiviral defense and individuals with impaired or reduced production of them possess higher susceptibility to viral infections. IFN-α and IFN-γ work by binding their receptors and activating downstream antiviral pathways involving the dsRNA-dependent protein kinase (PKR), the 2′, 5′ oligoadenylate synthetase/ RNase L, or the MxA protein. dsRNA, ssRNA, and CpG oligonucleotides are ligands for toll-like receptors (TLRs) and modulate antiviral immunity through TLR signaling pathways and IFN induction (Amlie-Lefond et al. 2005). It is also known that apart from directly interfering with viral replication, IFNs also affect antigen-presenting cells to stimulate antigen presentation to T cells through the MHC upregulation. As well, IFN-gamma has a number of overlapping functions with type I IFNs but in addition to that, it interferes with every stage of virus life starting with entry and replication to release, transmission and reactivation (Borden et al. 2007).

The first two placebo-controlled, double-blind studies evaluated the prophylactic efficacy of intranasal interferon α2 (IFN-α2) against induced rhinovirus (RV) type 39 infection in susceptible volunteers initially proved plausibility of these methods. The efficacy rates for multiple doses of IFN-α2 to prevent infection, virus shedding and colds specific for the RV type were 78%, 78% and 100%, respectively. The corresponding rates for one daily treatment were 45%, 64% and 75%, respectively (Farr et al. 1984). Three years later, in a double-blind study, 120 adult members of 46 families used 325 courses of intranasal spray over a six-month period, applying 5 million IU to the anterior nasal mucosa daily for seven days when another family member developed respiratory symptoms. Compared to a control group of 109 members from 49 families who used 319 seven-day courses of placebo spray, alpha2-interferon users experienced 33 percent fewer days with nasal symptoms and 41 percent fewer episodes of respiratory illness (Douglas et al. 1986).

The efficiency of these methods was supported by another study using inhaled interferon for four respiratory viruses (parainfluenza virus type 1-3, influenza B virus, adenovirus type 3, 7 and respiratory syncytial virus), participants in the interferon group had lower positive IgM antibody readings than the control group. The prophylactic efficacy of interferon against four respiratory viruses was as follows: influenza B (66.76%), parainfluenza type 1-3 (66.75%), respiratory virus - RSV (39.61%) and adenovirus (32.86%). The average preventive effectiveness of interferon was 50.27% (Yu et al. 2005). These results show that

this type of prophylaxis has a wide range of immune defense and may be even more effective than vaccination (see the examples of flu vaccinations).

When summarizing the results of studies of drugs based on interferon, conclusions can be drawn (Meng et al. 2020, Pereda et al. 2020, Turner et al. 1986, Yu et al. 2005):

- about good tolerance and safety of interferon (no cases of development of adverse events associated with the drugs used, or unforeseen side reactions have been registered)
- the use of both drugs in patients with a burdened allergic anamnesis (atopic dermatitis) did not aggravate the picture of their allergic disease.

Interferon and COVID-19

These antiviral defense mechanisms of both type I and type II interferons are also valid in the case of coronavirus infection. It was experimentally proven that the combination of type I and type II IFNs inhibits SARS-CoV plaque formation by 30-fold and reduces replication rate by 3000-fold even at 24 h post-infection (Sainz et al. 2004). Bearing in mind that one of the SARS-CoV-2 peculiarities is a prolonged incubation period, a preventative measure should provide enhanced production of both indigenous type I and type II IFNs, thus making it logical to use interferon inducers as the most appropriate preventative measure in the case of this pandemic.

One of COVID-19's peculiarities is that it has numerous clinical forms from an asymptomatic one to a highly severe one with lethal outcome. One of the simple explanations for this on the surface – it is the ability of a person's immune system to effectively respond to this viral challenge.

It is known that the severity of coronavirus infection depends on the type I interferons (IFNs) response timing relative to virus attachment, replication and propagation. Immediate production of one's own IFN-I or exogenous IFN administration can result in clearance of the virus or in a delayed and slowed multiplication, leading to lessening the sevirity of the symptoms. On the other hand, a delay in IFN-I response will most likely result in the increase of pro-inflammatory cytokine production and more severe outcomes (Channappanavar et al. 2019). The pattern of delayed IFN response most likely explains the tendencies in severity and mortality differences in coronavirus infected individuals varying by age and health condition; older population with existing health conditions such as cancer and cardiovascular diseases are more likely to get infected, to have severe course and to have higher probability of fatal outcome (Ioannidis et al. 2020). This is a major factor since with age the levels of IFN-I production decrease and people with health conditions, like mentioned above, have irreversible reduction in the amount of IFN-I produced. So, a younger generation having a "healthier" immune system with an ability to produce enough interferon can overcome this infection in a lighter form. On the other hand, people from the category of high-risk have aberrations in their immune response and one such problem is a delayed and ineffective response in terms of interferon synthesis.

IFN as a means of defense against COVID-19 has recently attracted considerable attention. It was shown in a clinical study (Turner et al. 1986) that prophylactic intranasal administration of interferon to volunteers exposed to coronavirus 229E (causing coronavirus cold) effectively prevented the infection (73% infected in placebo group vs. 41% in IFN group). Moreover, among infected, the individuals from IFN group had on average 2.5 times less severe symptoms as well as the shorter infection duration. A study published in June this year and involving 2944 participants taking intranasal interferon and 2035 people in the control group (Meng et al. 2020) shows that intranasal interferon has 100% protection efficacy even among medical personnel of high risk (i.e. those working directly with patients with serious forms of COVID-19). In the same publication, it was shown that medical personnel not using this type of protection were infected in almost all cases. At the same time, it was shown in another study (Pereda et al. 2020) that the combination of interferon-alpha 2b and oral antivirals (lopinavir/ritonavir) with chloroquine resulted in full recovery of 95% patients compared to 26% in the group receiving same medications with no interferon.

There is another not well-known beneficial effect of interferons. Apart from directly interfering with virus survival and replication, there is another indirect mechanism which is most likely responsible for these positive results. It is known that in the case of COVID-19 as well as SARS, the complement component of the immune response is responsible for the acute proinflammatory response. In COVID-19 patients, severe diseases and death are associated with the following scenario. Severe pro-inflammatory responses resulting from maladaptive immunity induces pro-inflammatory cytokines with blood neutrophils and monocytes released into the bronchi. These cells cause lung tissue damage leading to disturbed air-lung barrier. This damage results in thrombotic microangiopathies that lead to a patient's death (Risitano et al. 2020). It was also shown that C3 component activation is associated with acute respiratory distress syndrome (ARDS) in SARS while animals deficient in this component do not demonstrate that level of respiratory disfunction as observed in wild-type animals. Same association between C3 activation and lung damage was shown for SARS-CoV-2 while treatment with complement activation blockaders led to rapid and significant improvements in patients with COVID-19 (Risitano et al. 2020).

Interestingly, both type I and type II IFNs were shown to inhibit complement activation by binding to C3 component (Lebedeva and Kozlov 1997). This can possibly be explained by the affinity of IFNs toward the receptor of C3 via CR2/CD21 receptor present on IFNs (Delcayre et al. 1991).

Conclusions

The current situation with COVID-19 shows that in all situations like SARS, MERS, and COVID-19, we will always meet a new threat without having a specific defense. It is obvious that development of any vaccine would require substantial time with no assurance to have it eventually developed. If at some point the pandemic is over, there is a probability that the necessity of creating the vaccine will either disappear by itself, or even if the

vaccine is working, the next pandemic will be caused either by a new coronavirus or another unknown viral pathogen.

Based on the analysis done in this paper, we conclude:

- The method of protection using intranasal interferon has been known for more than 30 years;
- This method is non-specific and can protect against a wide range of viral pathogens, including influenza virus, ARI viruses, etc.;
- This method has been proven to be effective preventively in clinical trials with COVID-19;
- All types of interferon (including viferon), when applied nasally, will have a certain level of protection;
- The inclusion of intranasal interferons in the list of prophylactic drugs by some countries is scientifically based;
- Human use of intranasal interferons will reduce the risks of infection or disease with severe COVID-19.

Suggestions:

Since efficacy of intranasal interferons against a number of pathogens throughout a period of 37 years and against COVID-19 has been shown this year, this method of protection can be introduced in a short period while using a permitted off-label application approach.

And we would like to stress that the results of many studies including the one showing 100% protection against COVID-19 can help us to reverse the situation for the better even before a new vaccine is developed and tested.

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Ethics and security

Ethics approval and consent to participate – not applicable.

Conflicts of interest

Authors have no competing financial, professional, or personal interests that might have influenced the performance or presentation of the work described in this manuscript.

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