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REVIEW ARTICLE

Measles vaccines may provide partial protection against COVID-19

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Abstract

In December 2019 a new coronavirus COVID-19 was identified in China then spread all over the world. WHO defined China and Italy as the epicenters for COVID-19. Insufficient vaccine coverage has been identified as a key causative factor in the most epidemic outbreaks. Vaccines generally raise specific immune responses to a targeted pathogen, but measles vaccines have recently proved the increased ability of the immune system to fight off pathogens other than measles. COVID-19 is proven to have similarities with measles. Such similarities may cause cross-reactivity between measles vaccines and COVID-19. For instance, comparing China and Italy for COVID-19 case and the death rates from late 2019 until Mars 25, 2020, Italy showed higher ratio of COVID-19 cases/population and a higher death rate than China. In contrast, Italy showed lower measles vaccination coverage than China. In this review, we hypothesized that the bystander immunity induced by measles vaccines may provide partial protection against COVID-19, decreasing the virus's ability to cause fatal symptoms and controlling the infection leading to full recovery. Accordingly, we suggest multi-center clinical trials to evaluate the possibility of induced partial protection by measles-containing vaccines against COVID-19.

Introduction

In December 2019, patients who suffered from cough, fever, and dyspnea with acute respiratory distress syndrome (ARDS) due to an unknown viral infection were reported in Wuhan, China. Virus genome sequencing of five patients with pneumonia revealed the presence of a previously unknown coronavirus (β-CoV) strain in all of them [1, 2].

Coronaviruses are enveloped viruses with a positive-sense single-stranded RNA genome (26–32 kb), which replicate in the cytoplasm of infected cells. There are four coronavirus genera (α, β, γ, δ) with human coronaviruses (HCoVs) detected in the α-coronavirus (HCoV-229E and NL63) and β coronavirus (MERS-CoV, SARS-CoV, HCoV-OC43 and HCoV-HKU1) genera [3].

The isolated novel β-CoV shows 88% similarity to the sequence of two bat-derived severe acute respiratory syndromes (SARS)-like coronaviruses, bat-SL-CoVZC45 and bat-SL-CoVZXC21, and about 50% similarity to the sequence of MERS-CoV [4]. The novel β-CoV

was then named "SARS-CoV-2" by the International Virus Classification Commission [5].

Viral structure

Viral particles are composed of four major structural proteins: the nucleoprotein (N), the small envelope protein (E), the membrane protein (M), and the large spike protein (S). The entry of coronaviruses into cells is mediated by the transmembrane spike glycoprotein S, which forms a trimer carrying receptor-binding and membrane fusion functions. The S protein (SP) also contains the principal antigenic determinants and is the target of neutralizing antibodies [6].

Coronaviruses Spike protein (SP)

CoVs use their spike (S) proteins for host recognition and subsequent membrane fusion to introduce their viral genomes into the host for replication. Preventing CoV infection by blocking S-protein binding to host receptors : angiotensin-converting enzyme 2 (ACE2) for SARS-CoV, dipeptidyl peptidase 4 (DPP4) for MERS-CoV and Glucose Regulated Protein 78 (GRP78) for SARS-CoV-2[7,8], therefore, represents the first line of defense[7].

CoV S proteins consist of 2 functional units, the S1 and S2 subunits, which are responsible for cell attachment and membrane fusion, respectively [8,9]. Mutations in the receptor-binding motifs (RBMs) or cleavage sites of CoV S proteins can lead to zoonotic spillover and alteration of cell/tissue tropism, as exemplified by SARS and MERS [10,11] .

The coronavirus SP is a class I viral fusion protein and considered the major viral regulator in host cell entry [12]. Viral fusion proteins have grouped into three different classes according to their structure and biochemical activation processes, where class I proteins are characterized by predominant α-helical secondary structures and a trimeric organization of their pre-fusion and post-fusion states [13,14].

One interesting aspect of the class I fusion proteins is the differences in activation of their fusion mechanisms, despite their conserved structures [15,16]. However, all fusion proteins in this class undergo major structural changes that allow the viral fusion peptide to contact and anchor into the target cell membrane, and the formation of the "trimer of hairpins" structure followed by the fusion of the outer membranes (hemifusion) and the formation of the fusion pore. To successfully induce fusion, proteolytic activation of the viral protein subunits is often necessary, and this can vary significantly between different fusion proteins [16].

Similarities between Coronaviruses and Paramyxoviruses

Paramyxovirus is any virus belonging to the family *Paramyxoviridae*. Paramyxoviruses have enveloped virions (virus particles). The paramyxovirus genome is made up of a single strand of negative-sense non segmented RNA (ribonucleic acid). An endogenous RNA polymerase is present as well as is necessary for the transcription of the negative-sense strand into a positive-sense strand, thereby enables proteins to be encoded from the RNA. The lipoprotein envelope contains two glycoprotein spikes, including designated hemagglutinin-neuraminidase (HN) and fusion factor (F).

Paramyxoviridae has two subfamilies, *Paramyxovirinae* and *Pneumoviri nae*, each of which contains multiple genera. Examples of *Paramyxovirinae* genera include *Rubula virus*, which is composed of several species of human parainfluenza viruses and the mumps viruses; *Avulavirus*, which contains the species Newcastle disease virus (of poultry) and Morbilli virus, which contains the agents that cause measles in humans. Species of *Pneumovirus*, which are responsible for the serious respiratory syncytial virus disease in human infants, are classified in the subfamily *Pneumovirinae* [17].

Coronavirus SP shares a common core with *paramyxovirus* F proteins [18], implicating mechanistic similarities and an evolutionary connection between these viral fusion proteins. The accessibility of the highly conserved fusion peptide at the periphery of the trimer indicates potential vaccine strategies to elicit broadly neutralizing antibodies against coronaviruses. Comparison with crystal structures of human coronavirus S domains allows rationalization of the molecular basis for species specificity based on the use of spatially contiguous but distinct domains [19]. Despite weak sequence conservation, the structure demonstrates structural similarity to paramyxovirus F proteins, thereby reinforcing the relatedness of their fusion mechanisms and their evolutionary connection, which provide a structural framework to rationalize the mode of antibodies neutralization targeting the conserved fusion machinery [19].

Cross-reactivity and cross-protection

Cross-reactivity is the reaction between an antibody and an antigen that differs from the immunogen. It is also referred to as cross-immunity or cross-protective immunity. Cross-protection is a phenomenon in which infections with a mild virus or viroid strain protects from disease resulting from a subsequent encounter with a severe strain of the same virus or strain [20].

Although cross-reactivity does not necessarily infer cross-protection, a few examples of cross-reactivity have been confirmed in humans, one of which involves influenza virus-specific CD8+ T cell and hepatitis C virus antigens [21].

Studies proved that humoral immunity elicited by huN1 (human H1N1 infection) can partially protect against H5N1 infection in a mammalian host, suggesting that a portion of the human population could have some degree of resistance to H5N1 influenza. This possibility could be induced or enhanced through immunization with seasonal influenza vaccines, which was confirmed by studies in humans [22].

Measles containing vaccines (MCV)

Measles virus (MV) belongs to the genus *Morbillivirus* of the family *Paramyxoviridae*. Although these viruses are distinct agents, they share certain antigens [23]. MV vaccine (MCV) is a live-attenuated negative-stranded RNA virus was proven to be one of the safest and most effective human vaccines. This vaccine is produced on a large scale in many countries and distributed at low cost through the Extended Program on Immunization (EPI), induces life-long immunity to measles after one or two injections. [24]

MCVs were first licensed in 1963. Since the 1980s, several live attenuated measles vaccines were developed, either as a monovalent vaccine or in combination with rubella, mumps, or varicella vaccines, or some combinations of these. When using the combined measles–rubella (MR) vaccine, measles–mumps–rubella (MMR) vaccine, or measles–mumps–rubella–varicella (MMRV) vaccine, the protective immune response to each individual vaccine antigen is largely unchanged [24].

Over the last decade, outbreaks of vaccine-preventable diseases have been reported in developed countries around the world. Measles outbreaks have been ongoing in the European Union, with most cases concentrated in Romania and Italy. Measles has been identified as a powerful indicator of the status of vaccination programs in a region, as outbreaks have been reported to quickly emerge as a result of underlying problems in the immunization routine.

Insufficient vaccine coverage has been identified as a key causative factor in most measles outbreaks. Italy accounts for over 30% of measles cases reported since 2017 in the European Union [24]. In Italy mean measles vaccination coverage from 1980 until 2019 is 84.5% .The majority of reported measles cases

in 2016 were of unvaccinated people. One-third of the cases were among children aged 1–4 years [25].

China is making significant progress in battling measles disease, according to a December report from the Centers for Disease Control and Prevention. From 2013-2018, measles vaccine coverage in the country was estimated at 99%. Measles incidence declined from 31 per million in 2015 to 2.8 in 2018; only one measles-associated death has been reported during 2018–June 2019 [26].

Reduction effect of Measles vaccine on all-cause mortality

Vaccines generally raise immune responses specific to a targeted pathogen, such as antibodies that bind and neutralize one type of virus but not others. But MVC vaccine may also increase the ability of the immune system to fight off pathogens other than measles. According to a recent study, receipt of MCV standard titer was associated with a reduction in all-cause mortality (relative risks 0.74:0.51 to 1.07%) from four clinical trials and (0.51: 0.42 to 0.63%) from 18 observational studies. A study suggests that receipt of MCV reduces overall mortality through their effects on the diseases that they prevent [27].

COVID-19 and measles vaccines

WHO defined China as the first epicenter for COVID-19, then Italy became the second with an even higher death rate. Comparing the number of COVID-19 cases and the associated death rates in China and Italy from late 2019 until Mars 25, 2020 [25, 28] showed that Italy has lower as significantly higher ratio of COVID-19 cases/population (57 in China versus 1,431 in Italy) and a higher death rate than China (2 in China versus 151 in Italy).

When comparing the measles vaccination coverage in the two countries, China (96.7%) had higher coverage than Italy (84%). According to this profile, we suggest that the significant higher COVID-19 cases/population ratio and higher death rate in Italy as compared to China may be, at least in part, due to the lower measles vaccination coverage in Italy than china.

Perspective

From comparing statistical data for measles vaccination coverage, COVID-19 cases and deaths, we suggest that the MCV may provide partial protection against COVID-19. This vaccination induces immune system to fight the infection, to decrease the virus's ability to cause fatal symptoms and to control the infection leading to full recovery. Consistent with our suggestion, routine childhood vaccination, such as BCG, has also been suggested to provide bystander immunity to combat COVID-19 [29,30] We suggest the following two mechanisms that explain the ability of MCV to cause partial protection against COVID-19. The first is that MCV may increase the ability of the immune system to fight off pathogens other than measles due to the generated bystander immunity that would enhance the overall immunity against the new coronavirus. The second is that COVID-19 is proven to have structure similarities with measles, which may cause cross-reactivity and immunity between measles vaccines and COVID-19, leading to partial protection against COVID-19 in vaccinated subjects.

Recommendations

We recommend designing multi-center clinical trials to evaluate the possibility of induction of partial protection by measles-containing vaccines against COVID-19.

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