v1: 14 November 2024

Commentary

A Harmless Avian Vaccine Virus Could Be Developed into an Off-the-Shelf "Antibiotic" for Viruses

Peer-approved: 14 November 2024

Qeios, Vol. 6 (2024)
ISSN: 2632-3834

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A repurposed apathogenic double-stranded (ds) RNA vaccine virus, the infectious bursal disease virus (IBDV), significantly upregulates the expressions of type I interferon (IFN) genes. IBDV superinfection therapy (SIT) has been proven to be safe and effective against hepatitis A, B, and C viruses (HAV, HBV, HCV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and herpes zoster virus (HZV). IBDV might be used to control most virus infections before adaptive immunity develops. The safety and efficacy of a reverse-engineered new IBDV viral drug candidate, strain R903/78, could be reconfirmed in herpes zoster patients in a short-term Phase I/II study. With an off-the-shelf, stockpiled R903/78 drug, many millions of deaths and a repeat of the US$12 trillion the world spent on COVID-19 could be mitigated.

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Holmes et al. predicted that during the next fifty years, an important area for research in virology will be the competition of viruses. Viral interference should enable the development of better strategies for virus control[1]. There is no need to wait fifty years because the idea of fighting fire with fire, i.e., using non-pathogenic viruses to control unrelated infections, has already been translated into a host-directed antiviral therapy and successfully tested against five different families of viruses[2].

The objective of this article, therefore, is to argue that the infectious bursal disease virus (IBDV) drug candidate, strain R903/78, could be developed into an off-the-shelf stockpiled post-infection antiviral drug with modest funding within a relatively short time. In the era of large-scale vaccine hesitancy and skepticism, a broad-spectrum oral affordable antiviral drug could complement vaccination and improve pandemic preparedness. Actually, vaccination alone will not be sufficient to control future pandemics caused by rapidly evolving RNA viruses. Let alone that the frequency of zoonotic diseases is increasing because people exert pressures on nature, particularly via the huge livestock industry[3][4][5][6].

Zoonotic diseases are some of the most common and/or most dangerous diseases, including influenza, rabies, Lyme disease, Lentiviral immunodeficiency viruses, Ebola, SARS, and plague. The ability of zoonotic pathogens to transmit to humans is behind the concept of One Health, postulating the interdependence between animal and human health and aiming at improving preparedness for emerging infectious diseases. Probably the greatest known zoonotic risk to human health worldwide is presented by pandemic influenza. In the past 106 years, there have already been four influenza pandemics, and experts predict that another influenza pandemic is inevitable. In a few months, a pandemic flu strain could infect around 30% of the global population and could result in 200 million deaths during its first wave[3][7].

 doi.org/10.32388/AZ4JZV.2

The primary carriers of influenza are poultry and pigs. Close to 20 billion chickens and 1 billion pigs are produced annually worldwide, which are the primary drivers of influenza pandemic risk to humans. The low-pathogenic strain of wild birds can be transformed into a highly pathogenic form that can cause mass mortality in poultry and, potentially, in people. Pigs serve as the genetic engineering laboratory of nature. They are ideal mixing vessels, combining existing strains of influenza from birds or other animals, and transmit them to humans, amplifying the pandemic risk. Livestock, therefore, is one of our 'blind spots in biodefense'[4]. After COVID-19, we no longer have to imagine what an influenza pandemic would look like[5].

The fighting fire with fire idea has already been tested during the 1960s and 1970s. Large-scale clinical studies involving more than 60,000 individuals demonstrated that existing live vaccines can indeed protect against unrelated infections[8]. The oral poliovirus vaccine (OPV) reduced the morbidity of influenza virus infection 3.8-fold. OPV vaccination also had an accelerating healing effect on genital herpes simplex virus infections. Based on these pivotal early studies, Chumakov et al. proposed that live vaccines may temporarily protect against COVID-19[9]. This prediction was confirmed by Yagovkina et al., who demonstrated that a single dose of bivalent OPV significantly reduced the number of COVID-19 cases in 1115 healthy volunteers (aged 18 to 65). This is consistent with the hypothesis that live attenuated vaccines can induce non-specific protection against off-target infections[10][11].

Clinical observations of natural viral interference paved the way for viral therapies. Hepatitis B virus (HBV) infection is often terminated after accidental coinfection by hepatitis C virus (HCV). HCV dominance over HBV could, in turn, be terminated following the eradication of HCV by direct-acting antiviral (DAA) therapy. Consequently, HBV infection is often reactivated. When both interfering viruses are pathogenic, the disease (e.g., hepatitis) persists. Apathogenic viruses could, however, be exploited to control acute or chronic viral diseases. Such intentional coinfection is the *superinfection therapy* (SIT)[12].

The IBDV drug candidate of SIT is orally administered to patients suffering from acute or chronic viral diseases. IBDV delivers its double-stranded (ds) RNA cargo into host cells, where the dsRNA activates the native antiviral interferon (IFN) gene defense system via Toll-like receptors (TLRs). IBDV strongly induces IFN-β and IFN-λ, while IFN-γ is not induced. As IBDV did not lyse several mammalian cell lines, inflammation and antiviral efficacy are separated. In such a way, the therapeutic window is opened up such that IBDV maximizes antiviral efficacy with only minimal side effects[13].

IBDV is not known to infect human beings naturally. Consistent with this, IBDV R903/78 replication in mice could not be confirmed from multiple oral delivery experiments. In the presence of a rapid neutralizing antibody response, a wide range of IBDV R903/78 tissue distribution indicated genome accumulation rather than viral replication[14]. This observation is consistent with clinical experience. IBDV superinfection therapy was effective in several decompensated chronic hepatitis patients, showing striking clinical improvement without side effects when large doses (up to a cumulative dose of 3×10^9 infective particles) of the viral preparation were administered continuously over a long period to ensure the maintenance of 'artificial viremia' by IBDV. This is, in turn, consistent with the observation that repeated administration of Newcastle disease virus (NDV) remained effective in cancer patients despite the presence of neutralizing antibodies[12][15]. Importantly, IBDV treatment never induced an excessive release of pro-inflammatory cytokines, even though chronic HBV or HCV patients with decompensated liver disease had high-level viremia, which is a key driver of the cytokine storm[13].

IBDV has been proven to be safe and effective in marmoset monkeys and more than 50 patients against hepatitis A, B, and C viruses (HAV, HBV, HCV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and herpes zoster virus (HZV)[16][17][18][19][20][21][22][13]. The immunostimulatory power of IBDV is obvious to the naked eye, when a severe herpes zoster ophthalmicus (HZO) infection of the first author of this paper was healed within a few days[21].

The Safety and Efficacy of Reverse Engineered IBDV R903/78 Drug Candidate Could Be Reconfirmed in Herpes Zoster Patients

Attenuated IBDV has been used safely for over 60 years in IBDV mass vaccination programs in the poultry industry. Although attenuated avian vaccine viruses carry only a very low risk of mutation-associated zoonosis, it is a legitimate concern for the regulatory authorities. Therefore, an IBDV vaccine virus was recreated by reverse genetics technology as an artificial

virus, the R903/78 drug candidate[14]. This virus can be produced without labor-intensive re-plating in the event of the appearance of contaminating quasi-species. Experts of the US National Institutes of Health-sponsored ACTIV public-private partnership concluded that the IBDV strain R903/78 shows merit as a potential treatment for COVID-19.

The crusting time of vesicles following a standard of care acyclovir monotherapy with acyclovir plus an add-on R903/78 combination therapy could be compared during a short-term (one week) Phase I/II study in herpes zoster patients as described in[22]. The long-term safety and efficacy of the R903/78 drug candidate could be evaluated in virally suppressed HBeAg-negative chronic hepatitis B (CHB) patients as described in[20]. Those CHB patients who could not achieve functional cure during R903/78 monotherapy should be treated by sequential ultra-low dose ipilimumab plus nivolumab therapy as described in[20][13].

Over the last fifty years, the paradigm-changing idea of using non-pathogenic viruses to control viral diseases was translated into experimental antiviral therapies. Notwithstanding, the therapeutic exploitation of viral competition has still been unfairly overlooked when another influenza pandemic is inevitable. The avian H5N1 influenza virus is currently spreading through dairy cows and other mammals with transmission to humans, demonstrating that high-density commercial farming of animals poses a major pandemic threat[23]. As the most high-risk pandemic threat is the flu virus, it should be prioritized for resources. Development of the R903/78 drug candidate into an off-the-shelf stockpiled broad-spectrum post-infection antiviral drug could mitigate future pandemic deaths. This way, a repeat of the US$12 trillion the world spent on COVID-19 could also be reduced[24].

Statements and Declarations

Funding

None

Authorship statement

The first author warrants that both authors have seen and approved the manuscript, contributed significantly to the work, and that the manuscript has neither been previously published nor is being considered for publication elsewhere.

Conflict of interest

Tibor Bakacs declares stock/stock options from HepC Inc. and he is also a shareholder of HepC Inc. Konstantin Chumakov has nothing to declare.

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Declarations

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.