How Antivirals Might be Linked to the Emergence of New Variants of SARS-CoV-2

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SARS-CoV-2, the virus that caused COVID-19 pandemic, is spreading fast around the globe. As of January 24, 2021, this world health threat has affected more than 96 million people globally, with over 2 million reported deaths. This disease causes symptoms such as fever, cough, lung inflammation, thrombosis, stroke, and renal failure [1]. To date, COVID-19 treatment methods were mostly ineffective, and currently other than the vaccines, there are no promising drugs [1]. A report that is published recently in Science indicates that SARS-CoV-2 may be mutated in immunocompromised individuals [2]. In his report entitled "U.K. variant puts spotlight on immunocompromised patients' role in the COVID-19 pandemic", Kai Kupferschmidt states "In June, Ravindra Gupta, a virologist at the University of Cambridge, heard about a cancer patient who had come into a local hospital the month before with COVID-19 and was still shedding virus". He also notes "the patient, who died in August, 101 days after his COVID-19 diagnosis, despite being given the antiviral drug remdesivir and two rounds of plasma from recovered patients, which contained antibodies against the virus. When Gupta studied genome sequences from the coronavirus that infected the patient, he discovered that SARS-CoV-2 had acquired several mutations that might have allowed it to elude the antibodies". Now, the findings of Gupta and his colleagues are published as a preprint in medRxiv "Neutralising antibodies drive Spike mediated SARS-CoV-2 evasion". Interestingly, the B.1.1.7 variant (UK variant) that spreads much faster than other strains, includes one of the mutations found by Gupta. Given this consideration, it can be hypothesized that the B.1.1.7 variant has originated in an immunocompromised patient who had a long-running infection. It seems that people with weakened immune systems, due to their long period of illness, provide a greater chance of adaptive mutations for the virus to escape from the immune system.

Our research team proposed low dose radiation therapy as an efficient treatment method for COVID-19 associated pneumonia in March 2020 [3]. At the same time we raised serious warnings about treatment methods that could lead the virus to evolutionary adaptive mutations. Many experts believed that due to the proofreading mechanism of SARS-CoV-2, low mutation rates were expected compared to that of other RNA viruses that similarly infect the respiratory system, exhibit similar symptoms, and infect their hosts via surface proteins (such as certain orthomyxoviruses including Alphainfluenzavirus, the RNA virus that causes influenza) [4]. Given this consideration, SARS-CoV-2 was expected to have a relatively stable genome. However, later it was shown, to what a great extent, mutant variants of the SARS-CoV-2, can increase the risk of spreading the disease. The emergence of new variants in the United Kingdom (known as 20I/501Y.V1, VOC 202012/01, or B.1.1.7, emerged with

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an unusually large number of mutations), South Africa (known as 20H/501Y.V2 or B.1.351, and shares some mutations with B.1.1.7), and Brazil (known as P.1, with 17 unique mutations, including 3 in the receptor binding domain of the spike protein) raised these global concerns. The fast-spreading B.1.1.7 UK variant that sounded an international alarm is supposed be transmitted to other countries by travelers from the UK [5]. Moreover, the previous emergence of a variant with a new spike protein, namely D614G that was associated with increased transmissibility of the virus, prompted health researchers to investigate the role of these variants in lack of success in effective management of the COVID-19 pandemic [6]. Now, there are growing concerns regarding whether a previous infection to a specific variant of the virus causes cross-reactive memory to another variant [6].

Furthermore, the issue of the mink infection in Denmark, that led to the death of an extremely great number of minks, and the new mink-associated SARS-CoV-2 variant with a likely decreased susceptibility to neutralizing antibodies amplified the global concerns about the mutations of SARS-CoV-2 and the emergence of new variants [7]. A major shortcoming of the findings of Gupta and his colleagues is not paying enough attention to the key role of antivirals such as remdesivir in driving the virus into adaptive evolutionary mutations. Mortazavi et al. have previously addressed this issue in detail [8]. Briefly, substantial evidence now indicates that 1) viruses are constantly mutating and evolving and 2) when an antiviral immune response cannot eliminate a virus, viral evolution is promoted [8]. Therefore, using non-robust antivirals might be linked to the emergence of new variants of SARS-CoV-2.

These recent results and emergence of new mutations suggest our previous contentions regarding antiviral induced mutations merit further review by prescribing physicians treating SARS-CoV-2. The application of low dose ionizing radiation therapy merits further consideration as a safe modality for treating this disease, in part because it is a method that minimizes the generation and propagation of novel viral mutations.

Conflict of Interest

None

References

1. Conti P, Caraffa A, Gallenga CE, et al. The British variant of the new coronavirus-19 (Sars-Cov-2) should not create a vaccine problem. *J Biol Regul Homeost Agents*. 2021;**35**(1). doi: 10.23812/21-3-E. PubMed PMID: 33377359.
2. Kupferschmidt K. U.K. variant puts spotlight on immunocompromised patients' role in the COVID-19 pandemic. *Science* (News). 2020. Available from: https://www.sciencemag.org/news/2020/12/uk-variant-puts-spotlight-immunocompromised-patients-role-covid-19-pandemic.
3. Ghadimi-Moghadam A, Haghani M, Bevelacqua JJ, et al. COVID-19 tragic pandemic: concerns over unintentional "directed accelerated evolution" of novel Coronavirus (SARS-CoV-2) and introducing a modified treatment method for ARDS. *J Biomed Phys Eng*. 2020;**10**(2):241-6. doi: 10.31661/jbpe.v0i0.2003-1085. PubMed PMID: 32337192. PubMed PMCID: PMC7166223.
4. Manzanares-Meza LD, Medina-Contreras O. SARS-CoV-2 and influenza: a comparative overview and treatment implications. *Bol Med Hosp Infant Mex*. 2020;**77**(5):262-73. doi: 10.24875/BMHIM.20000183. PubMed PMID: 33064680.
5. Du Z, Wang L, Yang B, Ali ST, Tsang TK, Shan S, et al. International risk of the new variant COVID-19 importations originating in the United Kingdom. *MedRxiv*. 2021. doi: 10.1101/2021.01.09.21249384. PubMed PMID: 33469591. PubMed PMCID: PMC7814837.
6. Klumpp-Thomas C, Kalish H, Hicks J, Mehalko J, Drew M, Memoli MJ, et al. D614G Spike Variant Does Not Alter IgG, IgM, or IgA Spike Seroassay Performance. *J Infect Dis*. 2020. doi: 10.1093/infdis/jiaa743. PubMed PMID: 33257936. PubMed PMCID: PMC7798976.
7. Sharun K, Tiwari R, Natesan S, Dhama K. SARS-CoV-2 infection in farmed minks, associated zoonotic concerns, and importance of the One Health approach during the ongoing COVID-19 pandemic. *Vet Q*. 2021;**41**(1):50-60. doi: 10.1080/01652176.2020.1867776. PubMed PMID: 33349165. PubMed PMCID: PMC7833041.
8. Mortazavi SAR, Mortazavi SMJ, Sihver L. Selective Pressure-Free Treatments for COVID-19. *Radiation*. 2020;**1**(1):18-32. doi: 10.3390/radiation1010003.

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