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Review Article

Specific Co-Relation between Bacille Calmette-Guérin Vaccine and Coronavirus

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***ABSTRACT*:**
The Bacillus Calmette-Guerin vaccine (BCG vaccine) intended to prevent tuberculosis in children and has been shown to induce a trained immune response in the body to fight against bacteria as well as other parasites and viruses. This knowledge has been shared to generate the idea that this vaccine can also offer protection against severe acute respiratory syndrome coronavirus-2 (SARS-COV-2). Some current articles have highlighted that countries with mass BCG immunizations seems to have a lower incidence of coronavirus disease 2019 (COVID-19) related to those without BCG immunization. There are yet no experimental proof of any such association and the world health organisation (WHO) is presently testing the theory with clinical trials on selected cohorts. Additional trials are required to back the claim that while waiting for a specific vaccine to be developed, BCG can serve as an alternative to boost non-specific immunity.
Key words: coronavirus, trained immunity, live attenuated vaccine, BCG.

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INTRODUCTION

The Bacillus Calmette-Guérin (BCG) vaccine was developed in the initial part of the 20th Century by Albert Calmette and Camille Guérin. The procedure involved sub-culturing dissimilar strains of Mycobacterium tuberculosis and M. bovis. Work started in 1908 and lasted 13 years, during which time over 200 subcultures of M. bovis were produced. In 1921, the BCG vaccine was used in humans for the foremost time.[1] The primary use of the BCG vaccine is to guard against tuberculosis, though it is far from flawless in this regard. The vaccine is supposed to decrease the risk of contracting tuberculosis by approximately 50%, although this number differs by population.[2] While the standard delivery of the BCG vaccine is by mouth, current research in rhesus macaques has specified that there may be better protection when the vaccine is delivered intravenously.[3] The BCG vaccine has shown potential in terms of its probable application to conditions other than mycobacterial infections, especially autoimmune disorders. It is believed that there is some degree of cross-antigenicity between mycobacterial and human antigens.[4] Assumed its capacity to mobilise the immune system, it shows that administration of BCG may help in the management of infections. Certainly, there is some amassed evidence that the BCG vaccine offers non-specific protection and decreases the morbidity and mortality rates of viral infections.[5] Currently, the BCG vaccine is not generally

administered everywhere. Some countries choose alternatively to detect active disease via the Mantoux tests and treat cases as they arise. BCG has shown some efficiency against viral warts where according to few studies the effect is around 40%. Likewise, BCG has shown some effect in the framework of herpes infections. According to researchers, around 19% of patients were herpes-free after three years, and 9% after six years.[6]

BCG AND CORONAVIRUS

The SARS-CoV-2 virus has cleared across the globe at what for some might consider a astonishing speed, but is fundamentally in accord with mathematical pandemic models.[7] It is the seventh type of coronavirus to infect humans and cause ailments. The other six members of the coronaviridae family-like SARS-CoV or MERS-CoV (Middle East Respiratory Syndrome Coronavirus) are also known for their pathogenicity with relatively higher mortality rate than that of SARS-CoV-2.[8] Considering the virulence of this particular virus, and the sternness of the COVID-19 respiratory syndrome that accompanies many incidences of infection, any protective strategy is of considerable potential benefit. There is the known effect of trained immunity, in which infection with one pathogen offers protection against other pathogens. This effect has been cited briefly with respect to the volume of the BCG inoculation to render the immune system prepared for viral infections.[9] As the BCG vaccine is already approved for human use, any human studies to determine efficacy would only require Phase III clinical trials, making this a striking option (foregoing Phase I and II trials can take a year off the development time of a vaccine). The BCG vaccine strains that are working in the immunization programmes of different countries vary widely. There is substantial data to indicate that BCG vaccination provides protection against a range of infections, not just the mycobacterium for which the vaccine was originally developed. A study that consisted of both BCG vaccination at birth and delayed vaccination evidenced that the decreased mortality rate of the vaccinated group was due to the BCG-based prevention of a variety of conditions, including respiratory infections, neonatal sepsis, and fevers.[5] Likewise, BCG vaccination of elderly patients over a period of three months was seen which resulted in a drop in the incidence of acute upper respiratory tract infections. BCG has also shown some potential as a non-specific immunotherapy for virus-mediated conditions, including viral warts and herpes simplex.[10]

DISCUSSION

Presently, not a single antiviral or antimicrobial treatment has been demonstrated to be useful for COVID-19. Merging more than three antivirals are not recommended. As of now, treatment options are primarily based on the previous encounters and results showing benefits in the treatment of SARS, Ebola, MERS influenza, and other viral infections.[11] Remarkably, the BCG vaccine can also improve the immune response to other vaccines. One study linking the administration of the BCG vaccine prior to the influenza vaccine showed that antibody titre to the latter was significantly enhanced.[12] This study also showed that, following the BCG vaccination, there was fast seroconversion and improved pro-inflammatory leukocyte response, and even a modulation of cytokine responses against dissimilar pathogens. Generally, a vaccine provides protection from a particular pathogen, by encouraging effector mechanisms directed to that pathogen. Though, live attenuated vaccines like the Bacillus Calmette–Guerin (BCG), an attenuated strain of Mycobacterium bovis, deliver protection not only to a specific pathogen, but also against unrelated pathogens, some of which cause acute respiratory tract infections.[13]

IMMUNE MECHANISM OF BCG

The fundamental mechanism for the BCG vaccination-induced non-specific protection is supposed to be facilitated via the induction of innate immune memory, or "trained immunity.[14] Trained-immunity inducing agents reprograms bone marrow hematopoietic stem cells and multipotent progenitors through epigenetic and metabolic changes, ensuing in a more vigorous response in differentiated innate immune cells, resulting encounter with a pathogen.[15] Of interest, in a randomized placebo-controlled human study, BCG vaccination was verified to encourage epigenetic reprograming in monocytes, conferring protection against experimental infection with an attenuated yellow fever virus vaccine strain.[16] In case of humans, indications obtained from laboratory and clinical experiments and studies suggests that BCG vaccination may have non-specific precautionary results against viral infections.[17] For example, in the BCG-vaccinated mice, improved production of interferon gamma (IFN-γ) from the CD4+ cells took place in order to prevent the infection from the vaccinia virus.[18] Numerous metabolic as well as epigenetic changes are accountable for causing trained immunity. Due to this trained immunity caused by these metabolic and epigenetic changes, many genetic regions are endorsed for encoding of pro-inflammatory cytokines.[19] Proinflammatory cytokines like Interleukin-1B (IL-1B), also known as leukocytic pyrogen have an improvement in their secretions on BCG vaccination. IL-1B is known to have a vital role in immunity against viruses.[20] The perseverance and immunostimulatory properties of BCG strains differ, their potential to induce trained immunity in vaccinated individuals could also theoretically vary. Since BCG vaccination was earlier demonstrated to avert acute respiratory tract infections even in the elderly, until a specific vaccine is developed, SARS-CoV-2 susceptible populations could be immunized

with BCG vaccines. Such an approach would also be appropriate for frontline health personnel.[10] New studies exhibited the mechanism of BCG vaccine and its non-specific effects at molecular level. There is a tenacious change induced in the conformation of chromatin in adaptive and innate immune cells due to the BCG priming. These changes benefit the immune cells in enhancing immunity against bacterial, fungal, mycobacterial and viral infections.[21] Presently, due to the absence of any tangible evidences stating the fact that BCG vaccine prevents the infection of SARS-CoV-2, WHO does not approve of using the vaccine for treatment of COVID-19. In spite the fact that studies and experiments conducted both on humans and animals have shown that the non-specific effects of BCG vaccine on immune system, the clinical relevance and proper classification of these effects are still not known. Epidemiological studies, that indicate fewer reported cases of COVID-19 in BCG vaccinated neonates, are predisposed by various factors including the burden of disease and differences in demographics of the country, testing rates for COVID-19 virus infections and phase of the pandemic in each country.[22]

CONCLUSION

Although BCG is known to have non-specific effects and also known to supplement the immune system against viral infection, yet there are no strong clinical evidences signifying that it might be a solution to cure COVID-19. WHO does not recommend the promotion of BCG vaccination for COVID-19 prevention, however WHO still continues to recommend BCG vaccination for new-born's in areas with high occurrences of Tuberculosis. Further experimental work needs to be conducted for elucidation of the fact whether BCG vaccine is a hype or a hope amidst the pandemic.

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