

REPURPOSING BCG VACCINE FOR COVID19 IMMUNITY

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ABSTRACT

Covid 19 pandemic has created havoc in the world. As on 20th September 2020, the virus has reached 216 countries affecting nearly 31711237 people and 960826 have lost their lives. Various modes of treatment with the use of Hydroxychloroquine, Doxycycline, Ivermectin, Vitamin C, Zinc, Favipiravir, Remdesivir, Dexamethasone, Itolizumab, inhaled interleukins and others are being tried with varying degrees of success. Randomized clinical trials are being undertaken in many countries. Vaccines against Covid19 are in different phases of clinical trials and development. Scientists are also attempting to repurpose other vaccines that may offer protection against Covid 19. BCG is one such vaccine, available in the armamentarium for use. Preliminary reports suggest that BCG will offer nonspecific heterologous protection to decrease the occurrence of Corona virus SARS CoV2 infection or may help in decreasing the severity of the disease. This effect is likely to be mediated through 'trained immunity' offered by cells responsible for innate immunity.

KEYWORDS: Covid19, BCG vaccine, immunity.

INTRODUCTION

Corona virus disease (COVID-19) has created pandemic in the world as declared by W.H.O. on March 12, 2020. It is a viral disease caused by SARS-CoV 2 virus and has affected large populations in 216 countries. There is no specific treatment available and management is empirical. On the backdrop of this novel corona virus (COVID-19-SARS-CoV2) creating a pandemic and resulting in lockdown of cities with sealing of the borders, it is an emergent need that the medical and scientific community undertake quick measures. This virus has made social, political, economic, financial, medical, and scientific fraternity to go in a state of emergency. The spread of the virus has been as fast as the dissemination of fear and false news. Rapid isolation measures (test, trace and treat), social distancing of two meters, hand washing with soap and water for 20 seconds or sanitizer and wearing of masks have restricted the spread¹. Yet, we have not found solutions to treat the disease when it has affected individuals despite many clinical trials on drugs and vaccines that the world is looking forward to. All this may take some time. It is therefore prudent to think of repurposing vaccines used

for control of some other disease and use them for Covid 19 prevention or decrease in severity.

METHODS

An attempt is made to find out which vaccine can be used in heterologous way to decrease Covid 19.

BCG is one such vaccine. BCG i.e. Bacillus Calmette Guerin was prepared by Professor Calmette and Guerin of the Pasteur Institute in Paris as early as in 1921. They attenuated the bovine strain of the tubercle bacillus by passaging through artificial media for 15 years prior to success in 1921. The virulent pathogenic strain became permanently non pathogenic, remained alive, & retained all antigenic properties; hence called the live attenuated vaccine. The vaccine was tried successfully in an infant in 1921. Since then many countries have used BCG to prevent tuberculosis. India started its use in 1948 and then the vaccine was included in expanded program of immunization in 1978. Birth dose of BCG is given to all newborns in the country under national immunization program. Many countries have adopted the practice of giving BCG. Some did not and some discontinued after its use for few decades.

There are many types of BCG vaccine.

Liquid BCG-It is a liquid vaccine kept by continuous culture of the organisms.

Freeze dried vaccine-It is prepared by lyophilisation of harvested bacillary mass of selected strength of attenuated bacilli. Two main strains are in use.

Japanese strain-172.It is shorter and more heat resistant. It elicits higher post vaccinal allergy.

Russian strain

Danish strain -1331. It is seen to give greater protection in guiney pigs.

INH resistant BCG. This was prepared for use in children who received isoniazid as chemoprophylaxis.

Mycobacterial and ribosomal RNA vaccine

Recombinant BCG

Reaction to BCG-When BCG vaccine is given to a newborn infant or a child whose body is challenged for the first time, two reactions occur. First is activation of T cells which then produce two cytokines like GIT and MIF. These activated macrophages are responsible for delayed hypersensitivity. After intradermal BCG, small wheal, redness and induration occurs within few hours which subsides in 6-8 hours. Within two weeks, local induration comes, followed by papule, pustule in 4-6 weeks, edema around, discharge of pus at around 6-8 weeks followed by scab and healing in 10-12 weeks. Axillary nodes may enlarge. This occurs in non tuberculous children. However, children who have active tubercular disease, T cells react immediately to the antigen in BCG vaccine and accelerated reaction starts in 48 hours with pustule formation in 5-7 days and healing by second week. This is termed 'accelerated BCG response' delayed hypersensitivity and is also used as BCG test synonymous to tuberculin test.

BCG offers protection against tuberculosis. A large number of studies have given varying degrees of protection. Early studies showed 80% protection in some parts of USA, 0% in Georgia, 31% in Puerto Rico, 14% in Alabama, overall protection was 13 %. Studies in India showed that in Chingleput the protection was nearly 0% at the end of 5 years but was 28% when children were followed for 12 years. In Madanpalle protection was 31%.² Udani and others found that protection offered by BCG was not so much in preventing occurrence of pulmonary disease but it prevented the spread to miliary tuberculosis or disseminated disease². Thus, the protective efficacy of BCG is found to be in containing the disease.BCG at birth is thus included in India's national immunization schedule.

Booster dose of BCG at 2-3 years was also found to be more effective.^[2]

BCG vaccine and heterologous immunity

Immune system comprises of two main components, innate immunity and adaptive immunity. Innate immunity is present at birth and occurs via monocytes, macrophages, neutrophils, dendritic cells and NK cells. They fight against an antigenic insult independent of lymphocytes. They do not have memory.

Adaptive immunity. This is not present at birth but occurs when the baby is exposed to antigenic insult by disease or vaccine. It is governed by lymphocytes T cells or thymus dependent cells responsible for cell mediated immunity and B cells producing antibodies. These cells have memory and respond whenever antigen exposure occurs in later life.

Most vaccines produce antibodies that give protection when exposed to the same bacteria or viruses in later life like measles, tetanus.

Recent hypothesis-Old concept that innate immunity does not have memory is changing rapidly for over the last few years. These innate immune cells are seen to respond to a repeat antigenic insult by producing immunity via what is called as 'trained immunity.' This is seen to occur via epigenetic changes in NK cells, macrophages and monocytes.

Both experimental models and proof-of-principle clinical trials show that innate immune cells, can provide protection against certain infections in vaccination models independently of lymphocytes. This process is regulated through epigenetic reprogramming of innate immune cells and has been termed "trained immunity."^[3] Moreover, several lines of evidence suggest that certain vaccines influence immune responses against either other vaccines, or pathogens not targeted by the vaccine. These effects have variously been called 'heterologous', 'non-specific' or 'off-target' effects. 'attributable to prevention of the disease(s) targeted by the vaccine. We also use the term 'heterologous' to describe the activation of lymphocyte responses (antigen-specific or non-specific) that are directed against non-target antigens.^[3] On this principle BCG is seen to offer nonspecific protection against many bacterial and viral infections.BCG has immunomodulatory properties against respiratory infections.In Guinea Bissau, BCG (Danish) was seen to reduce all cause neonatal mortality by 38 % by reducing deaths due to pneumonia and sepsis. In South Africa, BCG reduced respiratory tract infections by 73% in adolescents.^[4]

BCG is seen to reduce severity of infections by other viruses similar in structure to corona.virus.(RNA single stranded positive sense), eg. BCG reduced yellow fever vaccine viremia by 71% in Netherlands and reduced

severity of mengovirus (encephalomyocarditis virus) in two studies in mice.

Current evidence of BCG and protection against Covid 19

BCG vaccine has been thought to bring about epigenetic and metabolic changes which enhance innate immune system. Netherlands and Australia have undertaken randomized controlled trials on BCG in reducing incidence and severity of Covid 19. BCG Tokyo strain may be better than BCG Danish.^[4]

In one study on effectiveness of booster BCG vaccine by Iradj Amirlak et al⁵ in UAE, was performed on 280 individuals out of whom 71 received BCG and 209 did not receive BCG. Infection rate for Covid19 was 0% in the BCG group and 8.6% in control group (p=0.004). One study showed that mean of cases per population ratio is statistically significantly lower in 138 BCG-vaccinated countries versus 37 BCG-non-vaccinated countries. A systemic review showed that countries with no policy of BCG vaccination, such as Italy and USA, showed higher mortality associated with COVID-19 than countries with long-standing BCG vaccination policies, such as South Korea and Japan. However, another recent study among those who were born in Israel before and after the time of policy of BCG vaccination showed no statistically significant difference in the proportion of positive COVID-19 cases among the BCG-vaccinated group (11.7%) vs the -unvaccinated group (10.4%). Another regression analysis showed no actual relationship between BCG vaccination and reduced cases of severe COVID-19.^[6,7,8] As a limitation, all previous studies are observational.

Various attempts have been made to improvise the efficacy of BCG vaccine. Recombinant BCG vaccine is one such attempt. VPM1002 is a recombinant BCG (rBCG) in which the urease C gene has been replaced by the listeriolysin O (LLO) encoding gene (*hly*) from *Listeria monocytogenes*. Urease C drives neutralization of phagosomes containing mycobacteria by generation of ammonia, thereby inhibiting phagolysosomal maturation and contributing to the survival of mycobacteria inside the macrophage. Its depletion allows for rapid phagosome acidification, which promotes phagolysosome fusion and provides the optimal pH for LLO stability.^[9] The available preclinical and clinical data reveal that VPM1002 is immunogenic and may be better than BCG in terms of safety. VPM1002 could be a safe, well-tolerated and efficacious alternative to the BCG vaccine in the future. Serum Institute of India Pvt. Ltd. can meet the global demand for a BCG vaccine and is well poised to supply the new vaccine if efficacy trials are successful.^[8] While this vaccine progresses through efficacy trials, next-generation derivatives are being designed and tested in preclinical models aimed at optimizing efficacy and/or safety. Recent evidence on recombinant BCG vaccine seems promising. Serum Institute of India has currently

undertaken booster BCG vaccination in various clinical trials and it would be interesting to see its long term effects.

CONCLUSION

BCG vaccine offers some protection against development of Pulmonary Tuberculosis but definitely helps in containing the disease and prevents development of Disseminated disease like TB meningitis, miliary tuberculosis etc. BCG vaccination results in development of adaptive immunity (T cell mediated) and also innate immunity or trained immunity. BCG vaccine is known to protect by producing heterologous immunity against viruses and bacteria other than mycobacterium tuberculosis. This may help in Covid 19 infection. Preliminary reports are suggestive of the fact that BCG may decrease the severity of Covid 19 infection. Booster BCG may be of help. Recombinant BCG can prove to have better efficacy. Clinical trials are actively underway.

We declare no conflict of interest.

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