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REVIEW ARTICLE

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BCG for Prevenion of COVID-19 in Type 1 Diabetes and Other High-Risk Populations

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ABSTRACT

Bacille-Calmette-Guerin (BCG) is a>100 year-old biological vaccine with versatile contemporary applications. It is still used worldwide to protect against tuberculosis, upper respiratory infections, and childhood mortality. Heralded as the safest vaccine ever introduced, it is given to 120 million newborns each year in developing countries. At the beginning of the COVID-19 pandemic and before introduction of COVID-19 vaccines, at least 5 randomized, double-blind, placebo-controlled trials were launched to test BCG's efficacy against primary infection by SARS-CoV-2. One of those trials was expressly for type 1 diabetics, one of the patient populations at high-risk of morbidity and mortality from COVID-19. The trial found that multi-dose BCG was safe and 92% effective versus placebo against SARS-CoV-2 primary infection. BCG recipients also had fewer infections of any type, suggesting that the vaccine may also provide broad-based protection against future SARS-CoV-2 variants. Two other trials with a mixture of high-risk patients also found BCG vaccines were about 65% effective. These trials might have found even greater efficacy had patients been observed for longer periods and after higher vaccine doses. Three clinical trials with BCG in health care workers used the Danish BCG strain and these subjects were previously vaccinated with BCG or had latent tuberculosis. These trials showed no efficacy. The major limitation is that BCG in adults takes 1-2 years to start to take full effect in adult populations. But once benefits appear, they may last years-to-decades according to other studies. In this review, we summarize the randomized clinical trial evidence surrounding BCG's use against COVID-19 and possible mechanistic underpinnings. We argue in support of BCG's use in patients with type 1 diabetes, especially because they are at high-risk of infections such as SARS-CoV-2 and the efficacy for the current vaccines is poor withbreakthrough infection after COVID-19 vaccination.

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Introduction

The Bacille-Calmette-Guerin (BCG) vaccine may broadly protect humans from infectious diseases. Originally introduced >100 years ago for tuberculosis prevention, BCG consists of a live attenuated version of the bacterium that causes tuberculosis in cattle (*Mycobacterium bovis*). It provides protection against Mycobacterium tuberculosis, the strain that causes human tuberculosis, in about 50% of recipients for a period of 10-20 years, according to meta-analysis [1]. As early as 1931, one the founders of the vaccine, Albert Calmette, observed that the BCG vaccine had broader infectious disease benefits beyond tuberculosis: it curtailed childhood mortality (unrelated to tuberculosis) by four-fold [2]. Since then, research has established that BCG protects against upper respiratory tract infections, leprosy, malaria, viral, and bacterial infections [3-17]. The BCG vaccine also has therapeutic efficacy. It has been used since the 1970s to effectively treat bladder cancer [18,19] and, after a long follow-up period, it has therapeutic benefit for two autoimmune diseases: type 1 diabetes [20,21] and multiple sclerosis [22, 23].

Considering BCG's wide-ranging infectious disease benefits, it was no surprise that, at the origin of the COVID-19 pandemic in 2019 and before the introduction of COVID-19 vaccines in mid-2021, a worldwide effort would be launched to determine whether the BCG vaccine could prevent primary infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Safety was not expected to be a concern given that BCG is one of the safest vaccines ever developed. Around 3-4 billion people have been vaccinated thus far with minimal side effects. BCG's safety is so remarkable that it is given to 120 million newborns annually [24].

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Literature review

This review summarizes the clinical trial evidence surrounding BCG for prevention against COVID-19 in type 1 diabetics and other high-risk populations. It also deals with mechanistic underpinnings and discussion of health care worker trials and ends with BCG's benefits for vaccine delivery.

BCG for COVID-19 protection in type 1 diabetics

Type 1 and type 2 diabetics are at higher risk of morbidity and mortality from COVID-19 than comparator populations, according to a meta-analysis of 40 studies with more than 18,000 participants [25]. Two more recent and nationwide studies, from the US and Greece, find that type 1 diabetics, in particular, have up to 74% higher rate of COVID-19-related hospitalization, up to 4 times higher rate of ICU admission, and up to 6 times higher mortality than non-diabetics [26,27]. Diabetics also have higher rates of breakthrough infections by SARS-CoV-2, despite vaccination with viral vector or mRNA COVID-19 vaccines [28-30]. The reasons why type 1 diabetics, in particular, are at such high risk are not known, but a new study suggests that their immune T cells may not be properly activated to defend against infections [31].

In 2020, at the origin of the COVID-19 pandemic, we had underway a Phase 2/3 double-blind, placebo-controlled trial of multi-dose BCG for another purpose: the treatment of type 1 diabetes. Patients had already received 3 doses of BCG or placebo two years earlier as part of a 5-year-long study. We adapted this trial into a parallel study to see if BCG could protect against primary infection by the original strain of SARS-CoV-2. The parallel study followed patients from January, 2020 until April, 2021, a 15-month period before the introduction of COVID-19 vaccines. Participants had received neither COVID-19 vaccine nor BCG vaccine at birth. They also were tuberculosis negative.

We found that BCG was safe and was 92% effective compared to placebo in protecting type 1 diabetic from COVID-19 infection [32]. Moreover, the BCG group (*vs* placebo group) had fewer infections of any type, few infectious symptoms, and lower infection severity. This kind of broad infectious disease protection suggests that BCG also might be advantageous against new SARS-CoV-2 variants. The trial's strengths were multi-dose BCG, use of a potent strain of BCG (Tokyo-172), long follow-up period, and outstanding safety with no systemic adverse events or patient drop-outs. The major limitation was that the benefits did not start to become manifest until 1-2 years after dosing. Still, once they appear they may last for years to decades, based on research on other off-target effects [20, 33].

BCG for COVID-19 protection in other high-risk populations

Two other trials in high-risk populations reinforced our findings. The first, known as ACTIVATE-2, was a multi-center, double-blind, placebo-controlled, phase III randomized trial of BCG for protection against COVID-19 among high-risk patients (n=301) in 11 departments of internal medicine in Greece [34]. The high-risk patients were over 50 years old and had co-morbidities, the most common of which were vascular hypertension (25.7%), COPD (25.7%) and type 2 diabetes (18.9%). No type 1 diabetics were included. The 301 volunteers in the trial received either a single dose of BCG (Moscow strain 361-1) or placebo, and were followed for 6 months. The trial found a 68% reduced risk of symptom-based and/or laboratory-based COVID-19 infection compared to placebo (based on an odds ratio of 0.32 and a 95% confidence interval of 0.13-0.79). It did not study protection against other pathogens. But an earlier trial by the same investigators, known as ACTIVATE, reported that BCG (*vs* placebo) reduced the incidence of non-COVID upper respiratory tract infections in elderly individuals 65 years or older [8].

The second confirmatory trial, known as BRIC, was a phase 3, quadruple-blind, placebo-controlled, multi-center trial in high-risk adults (n=495; ages 18-60 years) in 3 hospitals in India [35]. Participation was excluded if patients had been vaccinated against COVID-19. Patients had these high-risk conditions: diabetes (50%), cardiovascular disease (32%), chronic lung disease (15%) and chronic kidney disease (15%). (The authors did not specify which type of diabetes mellitus.) A history of tuberculosis was detected in 6% of the BCG group and 4% of the placebo group. Participants were given single-dose BCG (the strain was unreported) or placebo and followed for 9 months. The primary outcome, new COVID-19 infection, was assessed by two methods: definite COVID-19 by cartridge-based nucleic acid amplification, or probable COVID-19 by symptom profile. Secondary outcomes included severe COVID-19, hospitalization, and oxygen requirement. Severe COVID-19 was defined by a respiratory rate>30/min, oxygen saturation (SpO_2)<90% in room air, severe respiratory distress, or fulfilling criteria for acute respiratory distress syndrome. The authors did not report on whether participants had received BCG at birth.

The trial found that BCG did not prevent definite

COVID-19, but it did prevent probable COVID-19. The BCG group displayed a 62% decrease in probable COVID-19 (*vs* placebo), based on an odds ratio of 0.38 (95% confidence interval, 0.20-0.72). The BCG group had fewer cases of severe COVID-19, fewer hospitalizations, and fewer cases requiring oxygen. All three of these secondary outcomes showed 0 cases in the BCG group and 6 cases (2.4%) in the placebo group, each with a P value of .03. The trial found no vaccine-related serious adverse events (grade 3 or grade 4).

Mechanisms underlying BCG's beneficial immune effects

BCG's benefits against the viral pathogens responsible for respiratory disease have been the subject of a large body of mechanistic research. A consensus has emerged that BCG exerts its beneficial effects against respiratory viruses by boosting the innate immune system. The innate immune system not only reacts rapidly and nonspecifically to a pathogen, but also may react by a newly uncovered process of immune "memory" known as trained immunity [36, 37]. Under trained immunity, BCG vaccinations work through epigenetic reprogramming of histones of the immune system monocytes (key players in the innate immune system) to produce pro-inflammatory cytokines that lead to killing of a virus; when the reprogrammed monocytes meet the same virus again, they produce an even larger cytokine response. This "memory" response by monocytes is considered a novel feature of the innate immune system. Whether BCG-induced trained immunity specifically applies to SARS-CoV-2 is unknown [37].

Our laboratory has studied the mechanisms underlying BCG's benefits specifically for type 1 diabetics. The focus has been on the innate and the adaptive immune system, the other branches of the immune system best known for classic "memory" responses. For these overall immune effects with BCG in adults often the clinical responses are slow to take effect but offer long term protection and as above involve all limbs of the immune response. Also, the epigenetic gene signaling pathway with methylation and de-methylation effects of BCG are on many important signaling pathways of the immune system. The adaptive immune system consists of B and T lymphocytes. BCG's therapeutic benefits for type 1 diabetics may emerge from its actions on a subset of T cells where the density defects in correct signaling are corrected over a 3 year course for improved signaling. BCG affects their immune and metabolic signaling pathways through epigenetics [21,38]. A central player in the adaptive T cell "memory" response is the T Cell Receptor (TCR). The TCR learns to recognize a specific pathogen and becomes activated to respond expressly against that particular pathogen. We have recently reported that the T cells of type 1 diabetics are not properly activated because of a striking reduction in TCR density [31]. Lower TCR density may help explain why type 1 diabetics are more susceptible to infection [39]. We attribute the lower density of TCR to hyper methylation of TCR-related genes. Hyper methylation blocks gene expression. Our research shows that BCG acts over an extended period to correct the TCR defect in type 1 diabetics. It does so by epigenetically de-methylating the hypermethylated sites. That process facilitates expression of TCR genes. With better functioning of the TCR, type 1 diabetics may be more capable of combating COVID-19.

BCG for health care workers

Two other double-blind, placebo-controlled trials of BCG were in health care workers, who were considered at high-risk by virtue of occupation. Both trials had negative findings. The first was of 1,511 health care workers at 9 Dutch hospitals who received either a single dose of BCG (Danish strain 1331) or placebo and followed for one year. The primary outcome, unplanned absenteeism for any reason, was no different between groups, as was the secondary outcome, COVID-19 incidence. There was also no difference in another secondary outcome, self-reported acute respiratory symptoms or fever [40,41]. The second negative trial -another randomized, double-blind, and placebo-controlled - was of 1000 health care workers at 3 South African facilities who received a single dose of BCG (Dutch strain 1331) and followed for one year. Nearly 100% of participants had received BCG at birth and over 70% had latent tuberculosis, both of which may have offered background protection against COVID-19. In this second negative trial, BCG was not found to protect against COVID-19, severe COVID-19 (hospitalization), or respiratory tract infections (incidence or severity). Still underway is a large, 1-year long international trial of BCG for health care workers called BRACE [42].

Discussion

Here we have summarized the evidence that BCG vaccination protects against COVID-19 in type 1 diabetics and other high-risk populations. BCG does not appear to protect health care workers but, we believe, the two trials were negative for reasons that minimized the possibility of finding an effect. First, health care workers are generally younger and healthier than high-risk patients. Second, health care worker trials were relatively short (both followed patients for one year). Studies of other off-target

BCG effects in adults find that benefits do not appear until at least 1-3 years post-exposure [20-23]. Third, the dose of BCG in our view was not sufficiently high (trials used a single dose *vs* the minimum of 3 doses we use). Fourth, the strain (Dutch strain 1331) used in both health care worker trials was less potent than the one we use BCG Japan (Tokyo 172) for type 1 diabetics. Fifth, in both health care worker trials, participants in the treatment and placebo groups had prior BCG vaccination at birth, which would tend to obscure the possibility of finding of an effect because vaccine protection lasts for decades.

The reason why the ACTIVATE-2 and BRIC trials were successful with an even shorter follow-up period than the health care worker trials was, in our view, because both were enriched with high-risk patients. Had these two positive trials of high-risk patients been longer in duration, and had patients received multi-dose BCG with a potent strain, their efficacies of 62-68% might have been even higher. Our use of multiple doses of a potent strain and an observation period of 1.5 years found an efficacy of 92%.

In summary, we believe that BCG vaccination offers multiple benefits for type 1 diabetics and other high-risk groups as demonstrated by the recent RCT data. First, BCG has an enviable safety record stretching back 100 years. Its use in neonates worldwide is likely to undercut vaccine hesitancy. Second, BCG is highly affordable (about 10-75 cents a dose). Third, high-risk conditions are common in developed countries. In the US, the presence of at least one of the high-risk condition (including being>65 years) affects 75.4% of the population, according to nationwide data from the US National Health and Nutrition Examination Survey (NHANES) [43]. Fourth, BCG's benefits are likely to be durable. Benefits may last years to decades [20, 33], versus months with the mRNA vaccines [44]. The long-lived nature of the BCG response may be due to proper functioning of the TCR and to direct gene methylation re-programming, which occurs at a similar rate. In contrast clinical trials with high risk but healthy health care workers with the Danish BCG show no protection from COVID-19 disease so additional RCT need to focus likely on the most vulnerable populations [42].

Conclusion

Lastly, and perhaps most importantly, BCG may provide broad-based platform protection against future SARS-CoV-2 variants. This is an inference based on several types of studies. The clinical trial evidence from Faustman and colleagues (2022) showed that the BCG group exhibited fewer infections of any type, fewer symptoms of infection, and lower infection severity than the placebo group. Further, the inference is based on a broad array of epidemiological studies showing BCG's protection against a multitude of pathogens [3-17]. Existing mRNA vaccines narrowly target SARS-CoV-2's spike protein. Given the virus' high mutation frequency in the spike protein, mRNA vaccines are struggling to keep pace against new variants [45] and against a vaccine-weary public. The major limitation of BCG is that it does not work as swiftly as mRNA vaccines or live attenuated COVID vaccines. BCG's benefits take 1-2 years to become manifest. But once benefits do appear, they are likely to endure for years or longer.

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Conflict of Interest Statement

All authors have no conflicts of interest.

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