BCG vaccination as a treatment option for ME/CFS and Long COVID

Abstract

The Bacillus Calmette-Guérin (BCG) vaccine has notable “trained immunity” effects and was shown to have therapeutic effects in autoimmune diseases such as type 1 diabetes (T1D) and multiple sclerosis (MS). The BCG vaccine is the most commonly used vaccine worldwide. It may be a treatment option for Long COVID and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

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Introduction

COVID-19, like many viral infections, can lead to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)(Komaroff & Lipkin, 2023). Although many biological abnormalities are described for ME/CFS, it is still unknown what ultimately drives the disease process. There is evidence that viral reactivation or its immunological consequences may play a central role(Davis et al., 2023).

During viral reactivation, some of the viruses that all humans harbor within their bodies leave their latent (dormant) stage and begin to replicate. One of the viruses frequently implicated here is Epstein-Barr virus (EBV), a member of the family of the human herpesviruses(Ariza, 2021; Loebel et al., 2014; Ruiz-Pablos et al., 2023). In this respect, ME/CFS shows similarities with other immune-related disorders that have altered immune responses to EBV. These include systemic lupus erythematosus (SLE), Sjögren’s syndrome, and multiple sclerosis (MS)(Bjornevik et al., 2023; Jog & James, 2021). It has proven difficult to stop viral reactivation on a durable basis with classical antiviral medications(Kerr, 2019).

Immunomodulatory effects of the BCG vaccine

The BCG vaccine, in use since 1921, has several non-specific effects which all relate to its ability to modulate immune functions. These include anti-cancer effects(Redelman-Sidi et al.,

2014) and clinical mitigation of infectious diseases such as respiratory syncytial virus, human papillomavirus, herpes simplex virus(Moorlag et al., 2019), and malaria(Walk et al., 2019). The BCG vaccine also has disease-modifying effects in a range of autoimmune diseases.

For instance, in humans with early-onset type 1 diabetes (T1D), repeated BCG vaccinations (three shots within 2 years) were shown to induce long-term clinical remission in a double-blind, randomized controlled trial(Karaci, 2014; Kühtreiber et al., 2018). In early stages of MS, a single dose of BCG vaccine was shown to prevent progression to clinically definite disease when given after the first demyelinating event(Ristori et al., 2014). BCG vaccination was also shown to have preventive immune effects, including increasing resistance against childhood leukemia(Morra et al., 2017), atopic dermatitis(Thøstesen et al., 2018), juvenile T1D(Doupis et al., 2021) and, in patients with T1D, against COVID-19(Faustman et al., 2022).

Hypothesis

From these clinical observations it appears plausible that BCG vaccination could also have disease-modifying effects in ME/CFS or in the ME/CFS subtype of Long COVID. It is especially intriguing that BCG vaccination was shown to be therapeutically effective in other disorders where an aberrant immune response against reactivated EBV seems to play a central role, such as MS(Ristori et al., 2014).

Also notable are the documented antiviral effects of BCG vaccination on human herpesviruses, which suggests that BCG vaccination may be able to prevent reactivation of latent viruses, including human herpesviruses such as varicella zoster virus, cytomegalovirus, or EBV(Moorlag et al., 2019). There is a considerable body of evidence both from animal research and from human trials that BCG vaccination may be effective against reactivations of human herpesvirus 1(Pittet & Curtis, 2021). This has recently been confirmed in a subgroup analysis from a randomized controlled BCG vaccine trial(Pittet et al., 2023). However, in the latter trial, benefits were restricted to males.

It may also be worth considering that a different vaccine—a staphylococcal vaccine no longer on the market—is among the few interventions that have been shown to be effective against ME/CFS in the past(Zachrisson et al., 2002, 2004).

Immune system benefits for patients with ME/CFS and Long COVID

The biological effects observed after BCG vaccination may also explain why the vaccine could be effective in ME/CFS and Long COVID. For one, BCG vaccination was shown to affect regulatory immune cells involved in the dampening and balancing of systemic inflammation(Keefe et al., 2021; Koeken et al., 2020). This effect is thought to be based on the expansion of CD4+ T cells (Tregs). Indeed, BCG vaccination was associated with gradual demethylation (activation) of signature genes expressed in highly potent Tregs, including Foxp3, TNFRSF18, CD25, and IL2(Singhania et al., 2021). The fact that these changes occur on the epigenetic/transcriptional level and apparently involve bone marrow stem cells(Cirovic et al.,

2020) may explain the long latency between BCG vaccination and clinical effects in the T1D and MS trials.

The biological effects of BCG administration seem to also include metabolic changes in immune cells, with a shift of glucose metabolism from overactive oxidative phosphorylation toward accelerated aerobic glycolysis. This shift may explain the BCG vaccine's effect on blood glucose levels in the T1D trials(Dias et al., 2022) and its possible benefits in autoimmune and nervous system diseases(Faustman, 2020). This metabolic reprogramming may be of benefit in ME/CFS, where CD4+ and CD8+ T cells were found to have reduced glycolysis at rest (while CD8+ T cells also had reduced glycolysis following activation)(Mandarano et al., 2020).

BCG vaccination was also shown to induce tumor necrosis factor alpha (TNFα) with subsequent reduction of cytotoxic (including autoreactive) T cells(Ban et al., 2008). This could explain the effects of BCG vaccination in MS, with its pathogenetic background of autoreactivity (autoimmunity). A certain background of autoreactivity has also been found in ME/CFS and Long COVID(Bynke et al., 2020; Wallukat et al., 2021; Wirth & Scheibenbogen, 2020).

BCG vaccination as a trained immunity intervention

On a broader and more principal level, the effect of BCG might be in accordance with the "old friends hypothesis(Rook, 2023)". This hypothesis tries to explain why allergic and autoimmune diseases—such as T1D, MS, and ME/CFS—are on the rise in modern environments. According to these explanations, the defensive competence of the immune system has always been guaranteed and strengthened by constant encounters with highly diverse microbial species, both from the external environment and from within the body.

The latter component—the human endogenous microbiome—has included mycobacteria since the times of the Neanderthals. This may have helped to keep our endogenous microbiome in check—including many species of herpesviruses, which may even confer health benefits if kept in a latent stage(Barton et al., 2007). It has long been known, for instance, that tuberculosis itself protects from both T1D and MS(Airaghi & Tedeschi, 2006). From these considerations, it may be plausible to mimic these "old friends" with interventions now widely discussed as "trained immunity" interventions(Z. Hu et al., 2022; Netea et al., 2020). Here, BCG vaccination may be the most powerful option(Chen et al., 2023; Covián et al., 2019; S. Hu et al., 2022).

How to test the hypothesis

A feasible way to gather evidence on the effectiveness of BCG vaccination would be a large cohort study with random selection of patients who receive the BCG vaccine—which would be much easier and cheaper than a randomized controlled trial which would not be really "blind" anyways (due to vaccine side effects). Faustman Laboratory at Massachusetts General Hospital has performed rigorous BCG vaccine studies. Certainly, their expertise should be tapped in any study plans with BCG vaccination.

Unanswered questions

BCG vaccination is relatively cheap, safe, and easy to administer. Yet, there are quite a few unanswered questions and obstacles to overcome to gather high-grade evidence on this intervention.

1. How long will it take to see results? Effects may start to show months or even years after vaccination (in the MS trials, effects were noted after about 3 years)(Ristori et al., 2014).

2. Does receiving a BCG vaccination as an infant (BCG used to be a standard vaccination in many countries in the past) still confer protection decades later?

3. Which strain of BCG provides the best results in the vaccine? There are several strains of BCG with somewhat different effects on the immune system, but not all strains of BCG are available in every country.

4. Is there a way to conduct blind trials? BCG vaccination studies are difficult to carry out in a blinded fashion as BCG vaccination frequently causes a very notable skin reaction.

5. Do repeat vaccinations increase the effect? (There is some data to this effect. The T1D trials by Faustman et al., for instance, used a protocol of two repeat vaccinations 4 weeks and 12 months after the first shot.)

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