



The BCG Clinical Trial Program at MGH

Ongoing clinical trials for type 1 diabetes

OVERVIEW

Over the last two decades under the direction of Denise Faustman, MD, PhD, the Immunobiology Lab at Massachusetts General Hospital (MGH) has been investigating the potential of the generic bacillus Calmette-Guérin vaccine (BCG) to reverse various forms of autoimmunity, including type 1 diabetes. BCG is one of the oldest, safest and most affordable medicines ever developed, and has been shown in clinical studies to have the potential to tightly control blood sugars without hypoglycemia. The laboratory is now conducting a Phase II clinical trial, with additional trials planned.

HISTORY OF BCG

BCG is a vaccine that contains the avirulent tuberculosis strain *Mycobacterium bovis*. It has historically been given to protect against tuberculosis and, since its introduction in 1921, has been the most widely administered vaccine in the history of medicine. Considered to be extremely safe, BCG is on the World Health Organization's List of Essential Medicines and is given to roughly 100 million children per year globally. BCG is also one of the most affordable medicines, costing less than a dollar a dose in many parts of the world.

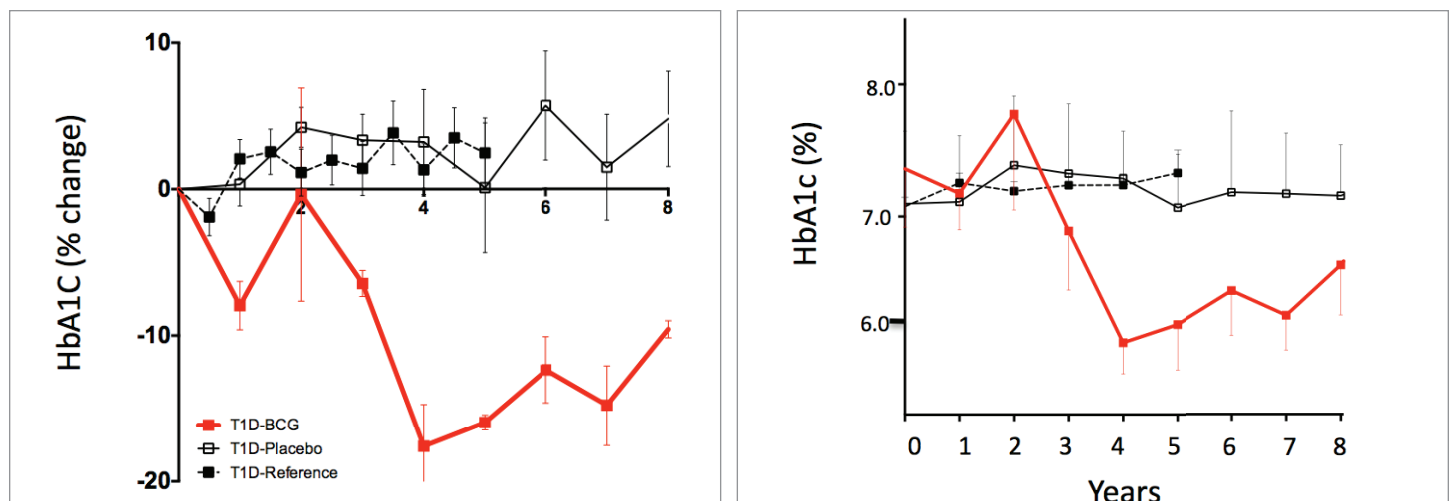
BCG AND TYPE 1 DIABETES

A Phase I trial of BCG showed significant efficacy in changing the primary biomarkers in established type 1 diabetes.

Repeat BCG Vaccination in Type 1 Diabetes

In the first MGH clinical trial in adult subjects with longstanding type 1 diabetes, the BCG vaccine (2 vaccinations 4 weeks apart) showed potential disease-modulating ability (i.e., death of autoreactive T cells, transient and modest restoration of insulin secretion, induction of regulatory T cells [Tregs]), but no clear clinical effects after 20 weeks of follow up. Long-term follow up of BCG-vaccinated patients in this program, however, showed a clear clinical effect, most importantly showing a statistically significant improvement in HbA1c (6.18 ± 0.34 vs placebo 7.07 ± 0.41) with no long-term hypoglycemia for greater than 5 years.

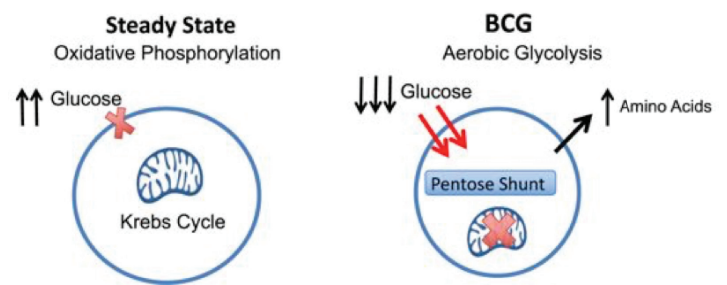
(Source: Kühtreiber WM et al. *npj Vaccines*, 2018).



NOVEL MECHANISMS WITH A VERY OLD HISTORY

The relationship between the increased incidences of allergy and autoimmune disease and the decline in chronic infections in modern societies has been well documented and is often described in the context of the “Hygiene Hypothesis” or the “Old Friends Hypothesis.”

These theories suggest that infectious diseases, in general, and life long bacterial exposure, in particular, may play an immunoregulatory role, including by inducing a cytokine called tumor necrosis factor (TNF) and potentially by upregulating a population of protective T cells called Tregs and killing the “bad” cytotoxic T cells. As societies have become cleaner, more urban, and less agricultural, there has been a reduction in infections and exposures coincident with an increase in the incidence of allergy and autoimmunity. It has been suggested that BCG may replace the impact of immunomodulating bacterial exposures lost in the move to cleaner societies. Epidemiological studies have also examined the impact of BCG vaccination in Turkish children and found that at least two doses had a protective effect against type 1 diabetes development compared to one or no vaccinations. Recent data from MGH suggests that a new and complementary mechanism in type 1 diabetes may be a BCG-induced shift in the process of glucose metabolism from oxidative phosphorylation (the most common pathway by which cells convert glucose into energy) to aerobic glycolysis. BCG induced aerobic glycolysis means the lymphocytes now can use large amounts of sugars, thus lowering blood glucose.



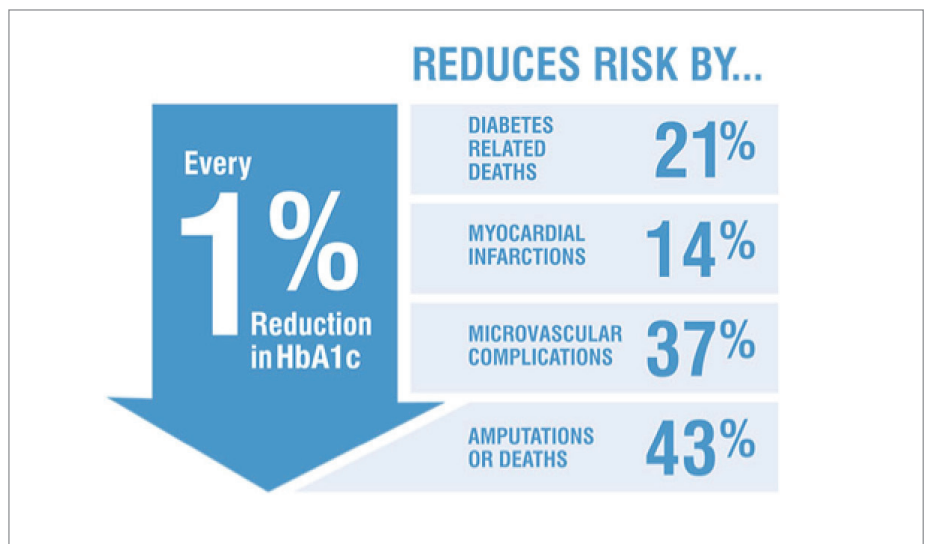
This is highly complementary to new data that BCG vaccination can also induce host DNA changes, thereby correcting the immune system of type 1 diabetics.

THE SIGNIFICANCE OF HbA1C

HbA1c refers to glycated hemoglobin and is a measure of overall average blood sugar levels over a period of months. Higher HbA1c is directly correlated with greater risks of developing diabetes-related complications such as blindness, heart attacks, strokes and renal failure. A significant lowering in HbA1c is a primary endpoint for diabetes clinical trials.

“The clinical effects and the proposed mechanism demonstrated are exciting and add to the emerging consensus that the BCG vaccine can have a lasting and valuable impact on the immune system. Multiple studies have now shown that BCG vaccination induces host DNA changes in immunity. BCG intervention and prevention trials underway around the globe may lead to a major shift in the prevention and treatment of infections and autoimmunity.”

Mihai G. Netea, PhD, Professor in the Department of Internal Medicine at Radboud University Medical Center in the Netherlands





ONGOING PHASE II TRIAL

A randomized, placebo-controlled Phase II clinical trial to test BCG as a treatment for type 1 diabetes is currently fully enrolled, and all 150 patients randomized to BCG or placebo have received at least two vaccinations. In addition to changes in HbA1c, the Phase II trial will measure changes in immune response, such as changes in C-peptide (the measure of endogenous insulin production) and patient insulin use.

PLANNED TRIALS

MGH is actively planning multiple trials in type 1 diabetes, including potential prevention and combination therapy trials. Two trials are currently in the formal planning stages and are beginning to register patients for future enrollment (Contact: diabetestrial@partners.org) when funding and approvals for the trials are completed.

Expanded Access Clinical Trial

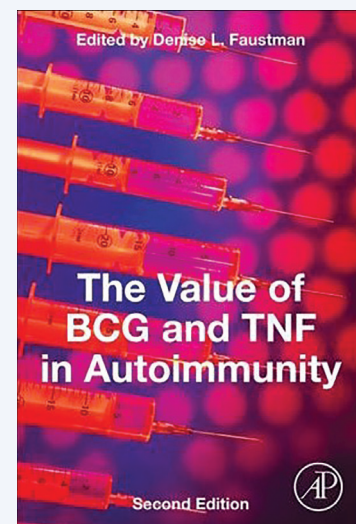
The United States Food and Drug Administration (FDA) has created a pathway for access to investigational new drugs that meet a significant unmet need through "Expanded Access" clinical trials. These trials are designed to make drugs available for patients with significant unmet needs prior to drug approval. Because there are no disease modifying therapies for established type 1 diabetes and BCG is a highly safe vaccine, MGH is initiating steps to begin an Expanded Access clinical trial so that additional patients can receive the BCG vaccination. Expanded Access trials are conducted with full regulatory oversight on an open-label basis. All enrolled patients will receive the investigational drug and be closely monitored and followed for the entire clinical trial.

Pediatric Trial

The Phase II pediatric clinical trial will test multi-dose BCG in children 4-18 years of age. We have proposed a randomized, double-blinded, placebo-controlled Phase II clinical trial with 150 participants (100 BCG and 50 placebo). Participants will receive two doses of intradermal BCG or placebo over five years. The trial will not interfere with the participants' pre-treatment standard of care. The endpoint will be a $\geq 5\%$ lowering of HbA1c for a duration of at least two years. There is hope that the transient C-peptide production seen in the older patients with a longer time since diagnosis will be clinically significant in younger patients who should have a great capacity to regenerate natural insulin production.

A GLOBAL MOVEMENT TO UNDERSTAND THE POTENTIAL OF BCG

The BCG clinical trial at MGH is part of a global movement to test the role of BCG in various forms of allergy and autoimmunity. Large pediatric prevention trials are underway in Denmark and Australia for allergy prevention and prevention of infections. A Phase III trial to reverse progression of multiple sclerosis is being conducted in Italy. We also discovered multiple new insights on how BCG and mycobacteria interact with our immune systems. Our working group has organized three conferences (London 2013, Verona 2015 and Athens 2017) and edited two editions of a book, "*The Value of BCG and TNF in Autoimmunity*" published by Elsevier. Learn more at: www.bcgandautoimmunity.org.





FREQUENTLY ASKED QUESTIONS

Were the studies controlled for changes in treatment or external factors such as exercise?

In addition to treatment and placebo groups the studies included large reference groups, to help control for changes in treatment and external factors. Several analyses were done to estimate the probability that receiving the BCG vaccine led to an improvement of blood sugars after 8 years as measured by a lower HbA1c level. The statistical tests designed to assess whether this result could have been found by chance found that the studies were highly statistically significant.

How does this durable clinical response compare to data from treatment utilizing insulin pumps and continuous glucose meters?

Insulin delivery by any mechanism will lower blood sugars, but unfortunately insulin alone can continue to lower blood sugars to ranges below normal, risking potentially lethal hypoglycemia. With insulin alone, the safe lowering of HbA1c requires a delicate balance between enough insulin to lower blood sugars but not enough to cause hypoglycemia (which can cause brain damage or coma). Continuous glucose monitors and insulin pumps can help maintain this balance but are expensive devices that need to be attached to the body and require continuous monitoring. Because of the risks of hypoglycemia, the target HbA1c with insulin pump usage is generally limited to 7 percent. BCG appears to have an endogenous effect on HbA1c that can lower levels below 7 percent without risk of hypoglycemia.

Are patients in this trial still using insulin?

We did not design the Phase I trial to see if patients could stop taking insulin. That question will be tackled in Phase II and the other studies we are designing. We have documented patients significantly reducing insulin use. These are observations, not clinical trial outcomes. The ongoing Phase II trial will closely monitor insulin use in all patients.

How does the treatment in the recently published studies differ from that in the Phase II BCG clinical trial?

All of the patients in the early studies received two doses of BCG, spaced 4 weeks apart, at the beginning of the study. The Phase II clinical trial patients all received two doses of BCG in the first year and will receive one dose a year for the following 4 years. We will also be tracking insulin use and key biomarkers like C-peptide in the Phase II patients.

What other clinical lessons have been learned from the BCG trial program?

As we moved from mouse studies to human clinical trials, there were several key steps we needed to make, including how to measure the death of autoreactive T cells, how to expand beneficial T cells called Treg cells and how to understand the clinical significance of low levels of continued insulin secretion on diabetes outcomes. A key question we are hoping to answer in Phase II is whether younger patients have the ability to regenerate insulin production as measured by C-peptide.

Will BCG be viable for everyone with type 1 diabetes?

Our trials so far involve adult patients with established type 1 diabetes – at least 2 years disease duration and in many cases more than 20 years duration. How BCG works in pediatric patients, how BCG works in new-onset patients and how BCG works in type 1 patients with more than 20 years of disease are all questions we hope to study in trials soon.

Could BCG be combined with other therapies?

How to improve and complement the immunoregulatory effect of BCG will be one of the questions we hope the diabetes community will help us answer. We believe we have demonstrated a mechanism and new basis for beginning a novel type 1 diabetes therapy. Complementary interventions that spur regeneration of insulin-producing cells or long-lasting/low-level insulin dosing options are all very interesting.

Who funds these clinical trials in type 1 diabetes or other autoimmune diseases trials?

The funding for the current BCG trials at MGH comes from the general public through philanthropic contributions. These trials do not currently have support from industry.

CONTACT AND ENROLLMENT INFORMATION

For more information about enrolling in the trials or supporting our research, please contact us:
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