The BCG Clinical Trial Program at MGH

Ongoing clinical trials for type 1 diabetes

OVERVIEW

Over the last two decades, the Immunobiology Lab at Massachusetts General Hospital (MGH) has been investigating the potential of the 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 lab is now conducting numerous trials including 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.

There are multiple strains of BCG produced globally that have documented differences in ability to induce an innate immune response. Over the last decade, MGH has established a source of FDA-standard manufacturing of what most experts believe is the most effective BCG strain in advance of a potential FDA approval and indication in autoimmunity.

BCG AND TYPE 1 DIABETES

A Phase I trial showed BCG has efficacy in causing a sustained drop in HbA1c in type 1 diabetes, as well as changing other primary biomarkers.

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+/-.34 vs placebo 7.07+/-.41) with no long-term hypoglycemia for greater than 5 years.

Source: Kühtreiber WM et al. npj Vaccines, 2018.

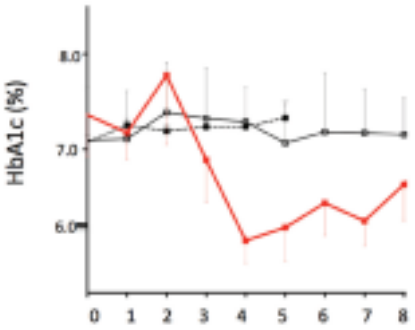
MGH BCG Trials Overview

Currently, 144 patients with type 1 diabetes have received BCG and are being followed. Another 100 are planned to be enrolled in early 2022.

	Total No. Subjects	BCG-Treated (n) Control/Placebo (n)	Double-Blind/ Open-Label	Time Followed to Date
Phase I + Crossover	52	9 43	Randomized, Double-Blind	5-10 years
Radiology Study	6	6 0	Open-Label	~3 years
Phase II Study	150	100 50	Randomized, Double-Blind	~3-4 years
Transition Study	29	29 0	Open-Label	2 years
Phase II Crossover	6	NA NA	Randomized, Double-Blind	3 months
COVID-BCG study*	143	95 48	Randomized, Double-Blind	18 months
TOTAL	236	144 93	--	--

Note: All BCG-treated patients have received at least two doses.

Red=BCG-treated T1D

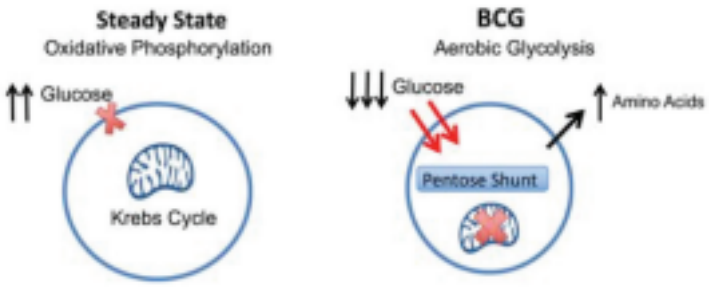


**The subjects in the COVID-BCG study are part of an adaptive study as part of the Phase II clinical trial.*

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 lifelong bacterial exposure, in particular, may play an immunoregulatory role, by inducing a cytokine called tumor necrosis factor (TNF), 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. 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 too much oxidative phosphorylation in type 1 diabetes (a pathway by which cells convert glucose into energy) to restored aerobic glycolysis, a pathway that uses more serum sugar. 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 IMPORTANCE OF TREGS

Tregs are important immune cells that are dysregulated in patients with type 1 diabetes. BCG therapy is associated with long-term, durable induction of Treg signature genes, helping Tregs function more normally along with other BCG-related improvements, such as improvement in HbA1c.

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

ECONOMIC IMPACT OF BCG FOR TYPE 1 DIABETES

Type 1 diabetes has dramatic financial impact on patients and families. The estimated direct medical costs exceed $20,000/year for an individual with type 1 diabetes. These costs do not factor in the indirect costs and quality of life issues that compound to make type 1 diabetes a tremendous financial burden. BCG is the only immuno-intervention in advanced trials for patients with longstanding type 1 diabetes and has demonstrated the ability to stably lower HbA1c. As a generic drug, it also represents an affordable intervention.

CLINICAL TRIALS

Over the last decade, MGH has conducted multiple BCG trials in type 1 diabetes. To date, over 200 patients with type 1 diabetes have been involved, including 144 treated with BCG. These trials have already demonstrated a clinically significant and durable response in established type 1 diabetes. Ongoing clinical trials include:

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.

Open-Label Juvenile Onset

MGH, through funding from Blue Cross Blue Shield of Massachusetts, has begun an initial clinical trial program to address BCG dosage, the role of age of onset on HbA1c lowering, and other questions so that additional patients can receive the BCG vaccination. These trials are conducted with full regulatory oversight in adults. All enrolled patients are receiving the investigational drug and are being closely monitored and followed for the five-year clinical trial. MGH is actively soliciting funding to increase enrollment.

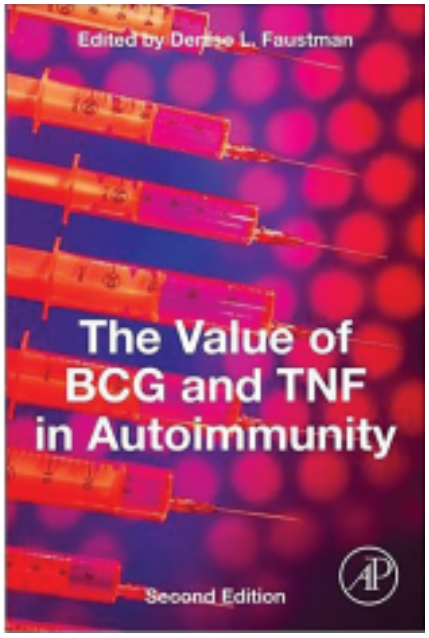
Pediatric Trial

The pediatric clinical trial will test multi-dose BCG in adolescents 11-18 years of age. MGH has 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 lowering of HbA1c. 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 save, stabilize and possibly restore natural insulin production. The pediatric trial will also test multi-dose BCG in 100 participants with new-onset type 1 diabetes (50 BCG and 50 placebo). MGH is actively soliciting funding to begin this program.

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. 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.bcgworkinggroup.com.



FREQUENTLY ASKED QUESTIONS

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

The Phase I trials were double-blinded and placebo-controlled to control for external factors. 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 reducing insulin use. These are observations, not clinical trial outcomes. The ongoing Phase II trial will closely monitor insulin use in all patients.

BCG has been tried for type 1 diabetes and other non-tuberculosis uses before with mixed success. Why are the MGH trials different?

Two key learning have come of these trials and MGH's collaborations. Frist, there are large differences among the strains of BCG in terms of immune response. The Tokyo strain MGH is using appears to be highly effective. Secondly, there is growing evidence that at least two vaccinations are necessary to induce an immune response in established diabetes or to delay onset. Multiple dose trials of the Tokyo strain have never been conducted prior to the MGH trials.

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 diabetes 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.

Can BCG prevent or delay onset of type 1 diabetes?

There have been no randomized trials to test the ability of BCG vaccinations to delay onset or prevent type 1 diabetes. Analysis of historical BCG vaccination records in Turkey showed that multiple doses of BCG significantly reduces the incidence of type 1 diabetes in children who received multiple doses compared to children with one dose or no doses of BCG.

CONTACT AND ENROLLMENT INFORMATION

For more information about enrolling in the trials or
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