

Questions and answers related to BCG vaccine research reported in *npj Vaccines* and presented at the American Diabetes Association Scientific Sessions

What are the key results published in *npj Vaccines* and presented at ADA?

The results published and presented in June 2018 are the long-term follow up of the BCG-vaccine-treated type 1 diabetes trial participants. The BCG-treated patients showed a durable and statistically significant lowering of HbA1c, the primary clinical marker used to evaluate diabetes therapies that measures average blood sugars. The BCG vaccine, originally developed for tuberculosis and known to be an extremely safe, also demonstrated no safety issues when used in type 1 diabetic participants.

How long did the HbA1c stay lowered after the clinical effect of the BCG vaccines was observed?

The HbA1c reduction was first observed 3 years after participants were treated with two BCG vaccinations four weeks apart, has remained persistently lowered for more than 5 additional years and to this day continues to be significantly reduced compared to placebo-treated study participants.

What is 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.

Did BCG vaccines correct the HbA1c to normal?

In this study, the BCG vaccines lowered HbA1c levels an average of 15-18 percent from the starting values after 4 years. BCG-treated participants' HbA1c averaged 6.1 at 5 years after receiving the vaccinations and 6.6 after 8 years, values close to the normal range. Prior to treatment with BCG, the average starting HbA1c values were 7.36.

What was the patient study group? Why are these results unique?

All of the reported patients were adults with existing type 1 diabetes for at least 2 years, and many patients had diabetes for over a decade at time of enrollment. These data are unique in that not only did repeat BCG vaccination dramatically lower HbA1c to a near normal range but the vaccine effect was durable and extended beyond 5 years without retreatment.

What is effect of the BCG vaccine on the immune system?

BCG has been known for over 30 years to boost a cytokine called TNF. In autoimmune diseases TNF is beneficial by directly eliminating self-reactive white blood cells (the autoreactive T cells that attack the pancreas in type 1 diabetes) as well as inducing beneficial immune cells called regulatory T cells (Tregs). BCG resets the immune system back to normal immunoregulation. Furthermore, the data in the paper report that BCG accomplishes this at the level of the patient's DNA, perhaps explaining why limited vaccines doses can have such a durable clinical effect.

How does BCG vaccine lower blood sugars to the near normal range?

The specific impact of repeat BCG vaccination on blood sugars in humans is driven by a novel mechanism – a systemic shift in glucose metabolism from oxidative phosphorylation to aerobic glycolysis (a state of high cellular uptake of glucose) on a tightly regulated level. Glucose uptake and its regulation at the cellular level prevent the potentially lethal hypoglycemia that can be induced by insulin treatment, since the cells stop transporting sugar when blood sugar is in the normal range

What is the BCG vaccine and how safe is it?

The BCG vaccine is a safe derivative of a strain of a mycobacterial organism. More than 100 years old, the vaccine was originally developed and is still used on a global basis to prevent tuberculosis in high-risk countries. Over the past century more than 3 billion people worldwide have received BCG vaccine, typically at birth. The World Health Organization has heralded BCG vaccine as the safest vaccine in the history of the world. Interestingly, mycobacteria have co-evolved with humans for over 100,000 years, but with today's cleaner modernized human environments, this mycobacterial species is typically not found within humans. This has led many to believe the "Hygiene Hypothesis" of why autoimmune diseases and allergies are on the rise in civilized countries – that humans may have lost evolutionary advantages conferred by living with safe versions of mycobacteria.

Is this data consistent with that of the Italian trials in multiple sclerosis, another autoimmune disease being treated with BCG vaccines in clinical trials?

Yes, the positive clinical impact of BCG that we report in type 1 diabetes patients is very similar to the clinical data being observed in new-onset multiple sclerosis patients treated with BCG. In the completed Phase II multiple sclerosis clinical trials, BCG-vaccinated patients similarly showed a 2- to 3-year delay in the clinical effect and since then, as in type 1 diabetes, have shown a durable and persistent clinical effect lasting greater than 5 years without the need to revaccinate.

Is this a cure for type 1 diabetes?

There are multiple definitions of a type 1 diabetes cure. These reported clinical trial studies, which involve limited doses of the vaccine, demonstrate that BCG vaccine creates a lasting blood sugar reduction to a near normal range that is not commonly or safely possible with insulin alone.

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 lead to 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. The recent data from MGH shows that repeat BCG vaccinations

can bring HbA1c down into the 6 percent range without additional mechanical devices and without continuous human-mechanical interface.

How does the amount of insulin used with BCG compare to insulin usage with continuous glucose meters and insulin pumps?

In general, the use of insulin pumps and continuous glucose meters increases the daily use of insulin. In contrast, the lowering of HbA1c with BCG vaccination has not been associated with increased insulin needs and in most cases is associated with decreased insulin usage. We did not design the Phase I trial with repeat BCG vaccines to see if patients could stop taking insulin. That question will be tackled in the Phase II and the other studies we are designing.

Are patients in this trial still using insulin?

The Phase I trial was not designed to track insulin use, but we have documented incidences of patients' significantly reducing or stopping insulin use for short time periods. These are observations not clinical trial outcomes. The ongoing Phase II trial will closely monitor insulin use in all patients.

What are the disadvantages of repeat BCG vaccines and who might not qualify?

Like any live attenuated vaccine, the BCG vaccine cannot be given to someone on immunosuppressive therapy nor to anyone on high-dose steroids. The vaccine requires a normal immune system to be effective and safe. Similar to the original disease process of autoimmunity, which is known to take a number of years to develop, in both type 1 diabetes and multiple sclerosis trials the BCG vaccine has taken a number of years for observable clinical effects – lowering of HbA1c or changes in brain disease activity. But the clinical effect in these human trials appears to be durable and long lasting beyond five-year observation periods.

How can more type 1 diabetes trials with BCG be conducted so more people can participate?

The rate at which these trials can move forward, as well as expanding research into more type 1 diabetic participants, is limited by funding, since formal clinical trials with FDA oversight are expensive. Donations are sincerely appreciated, and more information can be gained by emailing DiabetesTrial@partners.org.

How do I enroll in BCG clinical trials?

Please send an email to DiabetesTrial@partners.org and registration material will be emailed to you.

Have pediatric trials started so children can benefit from BCG?

Not yet. If we raise money for pediatric trials, we will start them. As noted above, BCG is typically administered at birth in Third-World countries, so safety is not an issue for future pediatric clinical trials. We do know that a single BCG vaccine given at birth, a time prior to the start of autoimmunity, is not protective against autoimmune diseases such as type 1 diabetes.

How many people participated in the *npj Vaccines* studies?

The *npj Vaccines* publication reports on 282 human research participants – 52 in BCG vaccine clinical trials and 230 whose blood samples were used for mechanistic studies. Of these total research participants, 211 had type 1 diabetes and 71 were non-diabetic control participants.

How does the treatment these patients received differ from patients in the MGH-based Phase II BCG clinical trial?

All of the patients reported in *npj Vaccines* and in the abstract presented at the American Diabetes Association meeting 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.

What is the status of the ongoing Phase II BCG clinical trials?

The FDA-approved Phase II clinical trial is fully enrolled (100 BCG participants and 50 placebo recipients). All participants have been enrolled for at least one year and have received at least two doses of the BCG vaccine.

Do you recommend all type 1 diabetics take BCG now?

We do not recommend that anyone take BCG for diabetes nor do we recommend any “off label” use of BCG. These results are reports from clinical trials and should not be confused with approval from the FDA.

Can BCG prevent type 1 diabetes?

There are interesting studies looking at the historic effects of multiple BCG doses on the incidence of type 1 diabetes in Turkey and Greece. Large pediatric trials are also underway in Australia and Denmark to look at the impact of this drug in resetting the immune system in allergies and in preventing other infectious diseases. The prevention question is partially answered in the Turkish study, in which BCG vaccination dosing could be from 0 to 3 vaccines and there was less diabetes incidence among participants receiving 3 vaccinations. There is also developing data in Greece on whether a childhood BCG vaccine changes the age of onset of diabetes.

How many patients are involved in the BCG clinical trial programs at MGH?

The MGH clinical trial program has been underway for more than 10 years. There have been hundreds of patients – diabetic and control – involved in treatment and additional study groups for the laboratory and clinical studies. To date more than 120 patients with existing type 1 diabetes have been treated with at least two doses of BCG. As reported in *npj Vaccines* and at the ADA 2018 Scientific Sessions, of 52 participants in either trial – followed for either more than 8 or up to 5 years, respectively – all treated groups had a statistically significant decrease in HbA1c, compared to placebo group participants or to a comparison group of diabetic patients receiving no study medication, with no reported episodes of severe hypoglycemic events, compared to placebo groups with long-term observations

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, the expansion of

beneficial T cells called Treg cells and the clinical significance of low levels of continued insulin secretion on diabetes outcomes.

Are there any active trials enrolling?

Yes. As of June 2018 we have eight clinical trials underway. Not only are we studying type 1 diabetic participants long-term to investigate the durability of the BCG clinical effects, but we also have many human studies ongoing on biomarker development, formal Phase II clinical trials, BCG strain comparison trials, drug stability studies with different BCG formulation formats, systemic glucose utilization studies with radiographic study and soon expanded studies into additional autoimmune diseases. Pending funding and FDA approval, MGH is planning several studies, including pediatric trials and trials in broader selections of long-term diabetics.

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

For all the currently ongoing trials at MGH of BCG for new autoimmune, allergic and infectious indications, the funding comes from the general public through philanthropic contributions. These trials do not currently have support from industry.

Why aren't more type 1 diabetics being treated with BCG, and how do I get into a BCG clinical trial?

Financial support drives the number of clinical trials we can offer. All type 1 diabetics interested in participating should email us at DiabetesTrial@partners.org for registration and follow up, since we will be able to expand these studies as grant money and public donations are received.

Will BCG work in other autoimmune diseases?

The potential in multiple sclerosis is well documented. We don't know if BCG will reverse other forms of autoimmunity. We are looking at fibromyalgia right now, and it would be interesting to see if other autoimmune diseases would respond to BCG.

When will BCG be approved for type 1 diabetes?

We do not know.

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 15 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 two decades of disease are all questions we hope to study in trials soon.

Does BCG work for type 2 diabetes?

There is growing evidence that BCG may play a role in metabolic disease, including type 2 diabetes. That data is extremely early but is a mechanism we are definitely interested in exploring.

Could BCG be combined with other therapies?

How to improve and complement the immunoregulatory effect of BCG will be one of the great 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.

How can I get a copy of the *npj Vaccines* paper?

We have paid to make the paper fully accessible to all so it is available online at <http://dx.doi.org/10.1038/s41541-018-0062-8> without a supplementary charge.