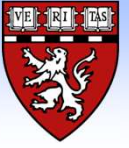




2022 Update on the BCG Clinical Trial Programs in Advanced Type 1 Diabetes

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Introduction

- The bacillus Calmette-Guérin (BCG) vaccine, introduced a century ago for tuberculosis prevention, is being tested in clinical trials as a treatment for type 1 diabetes (T1D) and other autoimmune diseases
- The BCG vaccine has two key beneficial effects as it relates to T1D¹⁻³:
 - BCG corrects underlying aerobic glycolysis defects in the white blood cells (WBC) of subjects with T1D
 - BCG-treated lymphocytes become a major consumer and regulator of blood sugars *in vivo*
 - WBC with accelerated glycolysis stop sugar transport when blood sugar is < 50 mg/dl
 - BCG restores the underlying sugar transport defects in the WBCs of those with T1D to levels closer to normal
 - Gradually (over 3 years) BCG induces potent regulatory T cells (Tregs) to suppress autoimmunity
- At our institution, multiple clinical protocols are underway testing BCG's ability to lower HbA1c, reduce insulin requirements and change day-to-day fluctuations in blood sugars
- Here we provide an update on the BCG clinical trial program at Massachusetts General Hospital (MGH): Enrollment numbers, study timelines and interim outcomes for key T1D biomarkers
- We also report on an observational study investigating BCG bladder cancer treatment and HbA1c

T1D Patient Enrollment & Follow-Up Timelines for BCG Studies

	Total No. Subjects	BCG-Treated (n)	Control/Placebo (n)	Double Blinded/Open-Label	Time Followed/Duration
Phase I + Crossover	52	9	43	Randomized, Double-Blinded	5 or 10 y/10 y
Radiology Study	6	6	0	Open-Label	~3 y/5 y
Phase II Study	150	100	50	Randomized, Double-Blinded	~3-4 y/5 y
Transition Study	29	29	0	Open-Label	2 y/5 y
Phase II Crossover	6	NA	NA	Randomized, Double-Blinded	2y/5 y
COVID-BCG Study*	143	95	48	Randomized, Double-Blinded	18 mo/18 mo
Phase II Pediatric Study*	150	75	75	Randomized, Double-Blinded	--

To date, 144 patients with longstanding T1D have received at least two doses of the BCG vaccine. Study groups include: 1) Long-term follow up of a Phase I study in adults to study the durability of lowered HbA1c values after BCG treatment; 2) Randomized, double-blind Phase II clinical trial in adults with longstanding T1D to demonstrate the reproducibility of Phase I findings; 3) Radiologic study to quantify and identify through FDG-CAT scans the organs/organ systems utilizing more sugar after BCG treatment; 4) Adult study comparing 2 vs 6 doses of BCG over 5 years of observation; and 5) Multi-center clinical trial of adolescents with ≥ 2 years T1D. * Currently enrolling.

Current Clinical Trial Updates

- An 8-year, randomized clinical trial in adults with longstanding T1D showed BCG vaccinations induced long-term improvements in glycemic control
 - In adults with longstanding disease (no pancreas C-peptide), the mechanism of blood sugar lowering is correction of aerobic glycolysis defects in WBC, which restores regulated sugar metabolism
- A randomized, double-blinded, placebo-controlled clinical trial with a 5-year follow up in adults with T1D will read out in about 1.5 years
- A double-blind, placebo-controlled clinical trial in older children (n=150) has started:
 - Multi-center trial with sites at MGH and NYU-Langone
 - Age 11 to <18 years, ≥ 2 years of T1D, stratified by C-peptide (+/-) at enrollment
 - Trial will evaluate the impact of BCG on restoring aerobic glycolysis, improving blood sugars and inducing Tregs to stop pancreas-driven disease
 - In those with significant C-peptide, it will also evaluate pancreas preservation

Retrospective Study: Effects of BCG Bladder Cancer Treatment on HbA1c

- We investigated whether BCG therapy for bladder cancer via intravesical instillation improves blood sugar levels in patients with comorbid T1D or type 2 diabetes (T2D) by analyzing three large US patient databases: United Healthcare (UHC, N=45 million), Massachusetts General Brigham (MGB, N=6.5 million) and Management Sciences Associates/Quest Diagnostics (MSA, N=263 million adults), identifying subjects with documented T1D (N=19) or T2D (N=106) undergoing BCG therapy for bladder cancer, and retrospectively assessing BCG's subsequent year-by-year impact on blood sugar trends

% Change HbA1c after BCG Instillation for Bladder Cancer

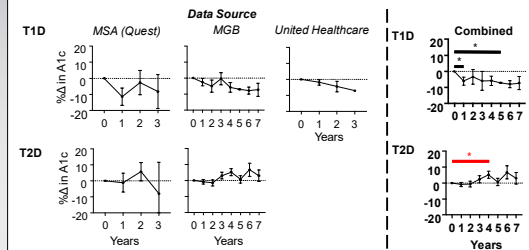


Fig 1. Lower HbA1c in T1D, but not T2D, post-BCG treatment for bladder cancer. For T1D, all three datasets show a reduction in HbA1c values (% change in HbA1c post-BCG instillation) and a near 10% decrease in A1cs at differing time points. The combined T1D data shows a statistically significant decrease in HbA1c year 1 and year 5 post-BCG ($p = 0.0304, 0.0136$). In contrast, MSA data for T2D shows no change and MGB data shows an increase in HbA1c values post-BCG instillation. The combined T2D data indicates a significant increase in year 4 after BCG instillation ($p = 0.0223$). (N for each dataset: MGB = 4, MSA = 9 and UHC = 6 for T1D; MGB = 97, MSA = 9 for T2D.)

Average Change HbA1c after BCG Instillation for Bladder Cancer

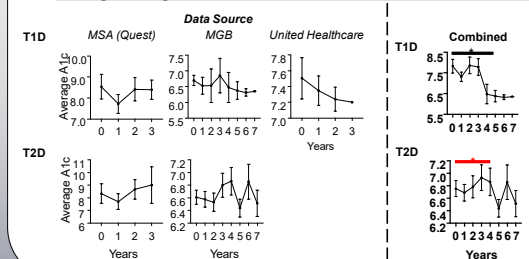


Fig 2. Decreasing trends in average HbA1c for T1D, but not T2D. In T1D, lower A1cs are seen for all three databases for subjects treated with BCG for bladder cancer. When all three T1D datasets were combined, a Student's paired t-test showed significance when comparing year 0 to year 5 ($p = 0.0133$). In T2D, the trend is in an upwards direction post BCG instillation, a significant increase when comparing year 0 to year 4 ($p = 0.0490$). (N for each dataset: MGB=4, MSA=9 and UHC = 6 for T1D; MGB = 97, MSA = 9 for T2D.)

Conclusions

- BCG vaccine therapy may provide a safe and affordable medical intervention in longstanding autoimmune diabetes; several clinical trials are underway
- In longstanding T1D, the primary mechanism for BCG vaccine efficacy is correction of underlying aerobic glycolysis defects in WBCs, thereby restoring regulated glucose transport for lowered and improved HbA1c values; BCG also gradually induces Tregs
- Elderly patients with very longstanding T1D who received BCG bladder cancer treatment show a similar gradual lowering of HbA1c, but this is not seen in those with T2D