NIH-funded first-ever clinical trial in immunotherapy-related diabetes

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UCSF Diabetes Center assistant professor **Zoe Quandt MD** and **Melissa Lechner MD PhD**, an associate professor at UCLA, have received a grant worth up to $7 million over five years from the National Institute of Allergy and Infectious Diseases (NIAID) to launch a first-in-human clinical trial evaluating whether a drug already used to treat autoimmune diseases can prevent or reverse immune checkpoint inhibitor-induced type 1 diabetes, a rare but often permanent complication of cancer immunotherapy.

Immune checkpoint inhibitor-induced type 1 diabetes develops in about 1% of patients treated with immune checkpoint inhibitors, drugs that have revolutionized the treatment for cancers over the last 15 years and earned researchers the Nobel Prize in 2018. Although the complication is uncommon, the destruction of the insulin-producing cells in the pancreas leaves patients fully dependent on insulin for the rest of their lives, a big hit to their quality of life.

“This is a devastating complication that occurs in the course of receiving life-saving treatments”, said Dr. Quandt, "We are thrilled to partner with Dr. Lechner at UCLA in launching a trial that may alleviate the one of the worst potential side effects of cancer immunotherapy."

Over 50% of people with diagnosed with an advanced cancer will be eligible for immune checkpoint inhibitors. At UCSF, that translates into over 1000 new patients a year that have been treated with immune checkpoint inhibitor therapies, and many of them who develop immune-related adverse events experience treatment interruptions, hospitalizations and long-term organ damage. The remarkable expansion in the use of immune checkpoint inhibitors as effective cancer treatments has led to an equally remarkable increase in the rates of autoimmune endocrine diseases tied to the unleashing of autoimmunity that can, unfortunately, sometimes be associated with these inhibitors.

The multi-center phase 1/2 trial will be conducted across the U.S. and will be the first prospective human study to test a treatment specifically aimed at the condition. Through this new multidisciplinary NIH award, UCSF and UCLA will be joined by City of Hope, University of Colorado and University of North Carolina to work collaboratively and comprehensively to determine if the use of the JAK inhibitor, baricitinib, will save the insulin producing cells that were under attack in recent onset checkpoint inhibitor type 1 diabetes. "We are positioned to greatly improve the lives, not only of individuals undergoing cancer treatment," said Chief of Endocrinology, Diabetes, and Metabolism, and Professor at UCSF Diabetes Center, **Suneil Koliwad MD, PhD**, "but also the broader population of people with autoimmune diseases, including type 1 diabetes.”

Drs. Lechner and Quandt decided on baricitinib given the promising combination of trials in type 1 diabetes, cancer care and mouse studies. Baricitinib has been shown to preserve insulin production in

conventional type 1 diabetes. Other JAK inhibitors were successfully combined with immune checkpoint inhibitors in some cancer settings with improved cancer response. Dr Lechner's lab reported a mouse **study** in *JCI Insight,* which was co-first authored by UCSF medical student Jessica Ortega, identified a critical immune cell group important to the autoimmune attack and showed that JAK inhibitors stopped the autoimmune attack on insulin-producing cells in the pancreas in mice and, in some cases, even reversed the damage.

The clinical trial, JAK Inhibitor to STOP beta cell loss in immune checkpoint inhibitor induced diabetes, also known as JAK STOP DM (AMIB-ICIDM-01), will test if these same results translate to humans. The team will assess the effects on insulin producing cells, while also monitoring the cancers that were being treated by the immune checkpoint inhibitors.

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