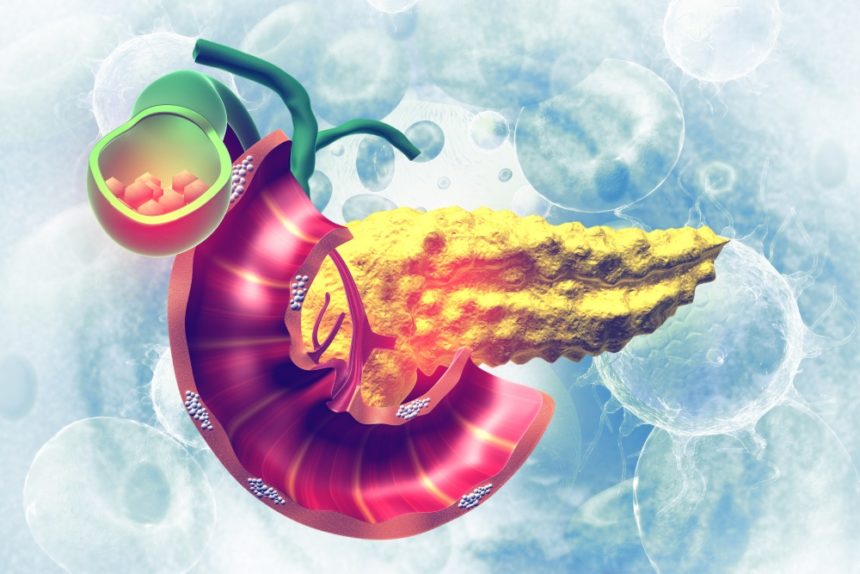
**Peptide Immunotherapy for Type 1 Diabetes: A Promising New Treatment**

[**Crystal Wong, MD**](https://www.endocrinologyadvisor.com/author/crystal-wong-md/)

Peptide immunotherapy offers a more nuanced approach that may reduce the risk for adverse effects in persons with type 1 diabetes.

Type 1 diabetes is characterized by the autoimmune destruction of pancreatic beta cells, leading to progressively decreasing insulin secretion. As beta cells die, hyperglycemia becomes more persistent, and most persons with type 1 diabetes have chronic hyperglycemia and often suffer from complications such as nephropathy and retinopathy. At present, treatment for type 1 diabetes targets hyperglycemia, but does not affect the underlying autoimmune processes.1

Immunomodulatory treatment, or immunotherapy, seeks to influence the immunological pathways that mediate beta cell destruction.1 “In the field of type 1 diabetes, we’ve been actively searching for ways to induce disease remission so that we can limit beta cell death, preserve endogenous insulin secretion, and limit the need for insulin injections,” Carmella Evans-Molina, MD, PhD, from the Center for Diabetes and Metabolic Diseases at Indiana University in Indianapolis, told *Endocrinology Advisor*.

Although more than 25 years has been spent investigating immunotherapy for type 1 diabetes, no agent has proven to be effective at inducing remission in [type 1 diabetes](https://www.endocrinologyadvisor.com/home/conference-highlights/easd-2017/t1d-risk-increased-following-influenza-a-h1n1-diagnosis-in-children/) with an acceptable safety profile. Advances in the understanding of autoimmune conditions have led to the development of antigen-specific immunotherapy (ASI) and a subset of ASI known as peptide immunotherapy. By using the short peptide epitope of a disease-related autoantigen instead of the whole antigen, peptide immunotherapy may curb the autoimmune process while avoiding undesirable adverse effects.1 For instance, peptide immunotherapy has shown promise in clinical allergy while avoiding the immunoglobulin E-mediated hypersensitivity associated with whole-antigen immunotherapy.2

“The way peptide immunotherapy works is a bit like when someone is allergic to dust mites or peanuts and receives treatment from an allergist to tolerize them against the allergen,” Dr Evans-Molina said. “With peptide immunotherapy, you’re administering small doses or small fragments of the peptide the immune system is reacting against, with the hope you can specifically turn off the immune system against that particular antigen.”

“An alternative approach is to try to target the immune system with drugs that globally turn off T- or B-cell responses. However, compared to peptide immunotherapy, this approach puts people at increased risk of immune suppression. Peptide immunotherapy offers a more nuanced approach that may reduce the risk of side effects because you’re not completely turning off parts of the immune system needed to protect us from infections. Rather, you are trying to educate the immune system to stop a specific immune response” she added.

**Peptide Immunotherapy: Proof of Concept**

A novel form of peptide immunotherapy is now being considered as a potential treatment for type 1 diabetes. A phase 1 study published in *Science Translational Medicine*examined the safety and metabolic effects of proinsulin peptide C19-A3, a peptide “representing an immunodominant region of proinsulin presented by the human leukocyte antigen (HLA) class II diabetes risk molecule HLA-DR4 (*DRB1\*0401*).”1

A prior study that examined proinsulin peptide C19-A3 in patients with chronic type 1 diabetes and the *DRB1\*0401*genotype showed that the treatment was well tolerated.3 However, because the participants had long-standing disease and absent circulating C-peptide, suggesting preexisting extensive beta cell destruction, the investigators indicated that additional studies in patients with new-onset type 1 diabetes were needed.1,3

Researchers, led by Mohammad Alhadj Ali, MD, PgDip, MSc, PhD, from Cardiff University in the United Kingdom, and Yuk-Fun Liu, MBBS, MSc, MRCP, from King’s College London in the United Kingdom, evaluated the safety and metabolic effects of proinsulin peptide C19-A3 in patients with a new diagnosis of type 1 diabetes (within 100 days), the *DRB1\*0401*genotype, and residual circulating C-peptide.1

A total of 27 patients were randomly assigned to proinsulin peptide C19-A3 administered intradermally every 2 weeks (high frequency) or every 4 weeks (low frequency), or to placebo. Patients were treated for 6 months and were followed up for 6 months posttreatment.1

Erythematous skin reactions at injection sites, without swelling or local wheal, were observed in 89%, 100%, and 50% of patients in the high-frequency, low-frequency, and placebo groups. No serious adverse events or hypersensitivity reactions were reported.1

Compared with placebo, the proinsulin peptide C19-A3 groups did not experience accelerated beta cell loss as measured by C-peptide area under the curve.1 “This is an important proof-of-concept study demonstrating the safety of this approach,” Dr Evans-Molina said.

“Moreover, there were some hints that individuals receiving the proinsulin peptide had less beta cell stress and stabilization of their C-peptide levels,” she added.

Patients receiving placebo experienced a significantly greater decline in C-peptide levels than the patients in the high-frequency and low-frequency groups at 3, 6, 9, and 12 months. Among both proinsulin peptide treatment groups, there were no significant changes in C-peptide levels compared with baseline at 3, 6, or 9 months.1

The daily insulin requirement increased by 50% by 12 months in the placebo group but remained unchanged in both proinsulin peptide groups. In fact, the average daily insulin dose at 12 months was significantly lower in the high-frequency and low-frequency groups than in the placebo group (*P*=.01 and .009, respectively).1

**Peptide Immunotherapy: The Future?**

According to Dr Evans-Molina, the proinsulin peptide C19-A3 study in new-onset type 1 diabetes provided proof of principle that peptide immunotherapy may offer a personalized approach to modulating the immune response in persons with type 1 diabetes. This study showed that tolerizing patients with the *DRB1\*0401*genotype against proinsulin, the autoantigen specific to this genotype, was safe and potentially feasible.

“Although this was primarily a safety study, there’s some evidence to suggest this particular peptide immunotherapy stabilized insulin secretion and had some beneficial effects on the beta cells,” Dr Evans-Molina said.

However, Dr Evans-Molina believes that the greatest potential for peptide immunotherapy in type 1 diabetes lies with disease prevention. “Next, we need to think about studying promising peptide immunotherapies in the early stages of the disease, when autoantibodies are present, but before significant beta cell loss has occurred,” she said.

“As you might imagine, when somebody loses enough of their beta cells to become diabetic, there may not be a lot of remaining beta cells to fight for. Also, we don’t know if peptide immunotherapy should be combined with drugs that target other aspects of the immune system. All of these possibilities and combinations need to be tested. Thus, it is critically important that we continue to fund studies aimed at preventing type 1 diabetes.”

In addition, stabilizing beta cell function may still be an important intervention for persons who have already been diagnosed with type 1 diabetes. “Any preservation of beta cell function is often very beneficial,” Dr Evans-Molina noted. “Individuals with type 1 diabetes who have residual beta cell function, often have diabetes that is easier to manage, fewer complications, and less hypoglycemia.”

*King’s College London holds a license agreement with UCB Pharma for peptide therapy development. Several investigators in the proinsulin peptide C19-A3 study in patients with new-onset type 1 diabetes (Alhadj, et al)* *are inventors on patents that cover peptides related to type 1 diabetes immunotherapy or have served as paid consultants for UCB Pharma for a phase 2 study design.*

**References**

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