Type 1 diabetes: Why managing insulin isn't enough anymore

Written by The Life Science Feed Editorial Team · Published 24 September 2026 · Edited by Mara Voss

Type 1 diabetes (T1D) has long been defined by the inexorable destruction of pancreatic beta cells, necessitating lifelong exogenous insulin. This autoimmune assault, often diagnosed after substantial beta-cell loss, leaves clinicians with few options beyond managing the metabolic consequences. But the emergence of therapies like teplizumab offers a new frontier, shifting the focus from mere symptom control to disease modification. Teplizumab, an anti-CD3 monoclonal antibody, targets the underlying autoimmune process, aiming to delay the onset of clinical T1D or preserve residual beta-cell function in newly diagnosed patients. This represents a fundamental re-evaluation of how T1D can be managed, moving beyond the established paradigm of insulin replacement.

KEY TAKEAWAYS

- The Pivot: Teplizumab offers a disease-modifying approach in type 1 diabetes, targeting the autoimmune destruction of beta cells rather than solely managing insulin deficiency.
- The Data: Clinical studies have shown that teplizumab can delay the onset of clinical type 1 diabetes in at-risk individuals and preserve C-peptide levels in newly diagnosed patients.
- The Action: Clinicians should consider screening at-risk individuals for T1D autoantibodies and evaluate teplizumab as a potential intervention to delay disease progression or preserve beta-cell function.

Type 1 diabetes is an autoimmune disease characterised by the immune-mediated destruction of insulin-producing beta cells in the pancreatic islets. This process is typically insidious, progressing through distinct stages marked by the presence of autoantibodies before symptomatic hyperglycaemia manifests. The conventional approach has been to initiate insulin therapy once clinical symptoms appear and the diagnosis is confirmed, but this intervention does not address the ongoing immune attack.

The disease mechanism involves a complex relationship of genetic predisposition and environmental factors, leading to a breakdown of immune tolerance. T-lymphocytes, particularly CD4+ and CD8+ T cells, infiltrate the pancreatic islets, recognising and destroying beta cells. This targeted destruction results in a progressive decline in insulin secretion, eventually leading to absolute insulin deficiency and the need for lifelong insulin replacement. Understanding these immunological pathways has been essential for developing therapies that aim to intervene earlier in the disease course, with the stake being the preservation of beta-cell function.

Targeting the Autoimmune Cascade

Teplizumab functions as an anti-CD3 monoclonal antibody, designed to modulate the immune system by binding to the CD3 receptor on T lymphocytes. This binding leads to a partial agonistic effect, followed by a reduction in pathogenic T cells and an increase in regulatory T cells. The net effect is a re-establishment of immune tolerance towards beta-cell antigens, thereby slowing or halting the autoimmune destruction.

The rationale behind this approach is to intervene before irreversible beta-cell loss occurs. By modulating the T-cell response, teplizumab aims to preserve endogenous insulin production, which can significantly impact disease management. Even a small amount of residual beta-cell function can improve glycaemic control, reduce the risk of hypoglycaemia, and potentially mitigate long-term complications. This is a significant departure from therapies that only replace insulin, offering a chance to alter the natural history of the disease.

The therapy is administered intravenously, typically as a short course. The transient nature of the T-cell modulation means that the immune system is not permanently suppressed, which is a critical consideration for long-term safety. This targeted immunomodulation seeks to re-educate the immune system rather than broadly suppress it, a key distinction from other immunosuppressive agents. The goal is to induce a state of immune tolerance specific to beta-cell antigens, preventing further autoimmune attack while preserving general immune competence.

The clinical application of teplizumab has focused on two primary populations: individuals at high risk of developing clinical T1D, identified by the presence of multiple autoantibodies and dysglycaemia, and newly diagnosed patients with residual beta-cell function. In at-risk individuals, the aim is to delay or prevent the onset of symptomatic disease. For those newly diagnosed, the objective is to preserve existing beta-cell function, extending the 'honeymoon period' and potentially reducing the burden of insulin therapy. This dual approach highlights the versatility of targeting the underlying autoimmune pathology.

Clinical Evidence and Patient Selection

Clinical investigations have explored teplizumab's ability to delay the progression to clinical T1D in individuals identified as high-risk. These individuals typically present with two or more T1D-related autoantibodies and evidence of dysglycaemia, but without overt symptoms requiring insulin. The intervention aims to prolong the period before full clinical diagnosis, offering patients and their families more time to prepare for disease management. The delay in diagnosis can also mean a longer period without the need for exogenous insulin, improving quality of life.

The mechanism of action, involving the modulation of T-cell activity, is central to these observed effects. By reducing the population of autoreactive T cells and promoting regulatory T cells, teplizumab helps to restore a degree of immune tolerance. This immunological shift is thought to be responsible for the preservation of beta-cell function, as evidenced by sustained C-peptide levels in treated individuals. Sustained C-peptide is a critical marker, indicating ongoing endogenous insulin production, which is a primary goal of disease-modifying therapies in T1D.

Patient selection for teplizumab is important, focusing on individuals in the earlier stages of autoimmune destruction. This typically involves screening for autoantibodies, such as GAD65, insulin, IA-2, and ZnT8, in relatives of patients with T1D or in the general population. Identifying individuals with multiple autoantibodies and impaired glucose tolerance allows for intervention before significant beta-cell mass is lost. This proactive approach is a significant shift from the traditional reactive management of T1D, where treatment begins only after symptomatic onset. For a deeper understanding of patient-clinician dialogue in managing severe hypoglycemia, refer to our previous coverage.

The safety profile of teplizumab has been a key consideration. Common adverse events include transient lymphopenia,

rash, and cytokine release syndrome-like symptoms, typically mild to moderate and manageable. These effects are generally transient and resolve without long-term sequelae. The balance between immunomodulation and maintaining overall immune competence is delicate, but the data suggest that teplizumab achieves this without undue risk of severe or opportunistic infections. The Oxford Handbook of Endocrinology and Diabetes provides further practical guidance on managing complex endocrine conditions.

Challenges and Future Directions

Despite its promise, the integration of teplizumab into routine clinical practice presents several challenges. One significant hurdle is the need for widespread screening for T1D autoantibodies, which is not yet standard practice in many healthcare systems. Identifying at-risk individuals requires a robust screening infrastructure and clear guidelines for who should be tested and when. Without effective screening, many eligible patients may miss the window for early intervention.

Another consideration is the long-term durability of the treatment effect. While studies have shown a delay in disease progression, the question of whether a single course of teplizumab provides indefinite protection or if repeat treatments are necessary remains. Further research is needed to establish optimal dosing regimens, the timing of re-treatment, and the long-term impact on beta-cell function and clinical outcomes. The cost-effectiveness of widespread screening and treatment also needs careful evaluation.

The precise mechanisms by which teplizumab induces immune tolerance are still being elucidated. While T-cell modulation is central, the full spectrum of immunological changes and their sustained effects requires ongoing investigation. Understanding these mechanisms more deeply could lead to the development of even more targeted and effective immunotherapies for T1D. This ongoing research is vital for refining current strategies and exploring novel approaches to autoimmune disease management.

The broader implications for T1D management extend beyond just delaying onset. Preserving even a small amount of endogenous insulin production can significantly improve the quality of life for patients, reducing the complexity of insulin regimens and mitigating the risk of complications like severe hypoglycaemia. This shift towards disease modification represents a new era in T1D therapy, moving beyond symptomatic management to address the root cause of the disease. The potential for understanding hypoglycaemia through CGM data further highlights the need for comprehensive management strategies.

> **CLINICAL IMPLICATIONS**
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> The arrival of teplizumab forces a re-evaluation of how we approach type 1 diabetes. For too long, the diagnosis of T1D has been a sentence of lifelong insulin dependence, with little hope of altering the underlying disease course. This drug, by targeting the autoimmune destruction of beta cells, offers a tangible opportunity to delay that inevitability, or at least preserve some endogenous insulin production.
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> Clinicians must now consider the practicalities of screening for T1D autoantibodies. Identifying at-risk individuals before symptomatic onset is paramount, but this requires a shift in current practice and potentially new guidelines for population-level screening. The investment in identifying these patients early will be essential to maximise the benefit of such disease-modifying therapies, with the stake being improved patient outcomes and reduced disease burden.

> But the conversation does not end with delayed onset. Preserving C-peptide, even modestly, can significantly improve glycaemic control and reduce the burden of insulin therapy. This translates to fewer hypoglycaemic events, better quality of life, and potentially a reduction in long-term complications. The economic implications of such a shift, both for healthcare systems and for patients, are substantial and warrant careful consideration. The challenge now lies in translating this emerging potential into widespread clinical reality. This means not only refining patient selection and treatment protocols but also educating both clinicians and the public about the benefits of early detection and intervention in T1D. The era of simply replacing insulin is slowly giving way to a more proactive, disease-modifying approach.

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