HHS Public Access

Author manuscript

N Engl J Med. Author manuscript; available in PMC 2022 April 11.

Published in final edited form as:

N Engl J Med. 2020 November 19; 383(21): 2078–2079. doi:10.1056/NEJMe2030472.

Whither Type 1 Diabetes?

Domenico Accili, M.D.

Department of Medicine and Berrie Diabetes Center, Vagelos College of Physicians and Surgeons, Columbia University, New York.

Since 1922, insulin has been the sole effective treatment for type 1 diabetes, which is now known to be the result of T-cell–mediated autoimmune destruction of pancreatic beta cells.[1] In 1982, the approval of synthetic recombinant human insulin by the Food and Drug Administration heralded an era of nimbler pharmacokinetics and delivery devices that yielded better outcomes. Yet, insulin-based treatments are increasingly complex, costly, and limited by the risk of hypoglycemia.

Three potentially complementary approaches are vying to become the standard of care for type 1 diabetes in the 21st century; these approaches include automated devices to deliver insulin (with or without other hormones) that are fully integrated with real-time glucose measurements (a so-called closed-loop system), implants of stem-cell–derived beta-like cells (with or without immunosuppression), and immunotherapies.[2] None of these strategies can be considered a cure in the terse, compelling sense, which was once conveyed to me by a patient as “something that I don’t have to think about every day,” because they all further medicalize management, thereby affecting a patient’s ability to strike a balance between disease control and lifestyle.

Building on its success in autoimmune disorders, targeted immunotherapy of type 1 diabetes leverages detailed knowledge of the process leading to beta-cell demise to modify the process of — if not to outright cure — the disease; the disease process is classified according to a staging algorithm in which patients are stratified according to genetic risk (stage 0), development of islet autoantibodies (stage 1), development of prodromal metabolic abnormalities (stage 2), and onset of clinical symptoms (stage 3).[3] Indeed, the failure to bring about a radical cure has spawned intermediate therapeutic targets. One such target is the preservation of the C-peptide response to a standardized meal test. Although the outcome of this test makes little difference with respect to a patient’s daily regimen, it has been shown in the landmark Diabetes Control and Complications Trial to correlate with a lower incidence of diabetic ketoacidosis, hypoglycemia, and glycemic variability, as well as lower insulin requirements.[4]

In this issue of the *Journal*, the T1GER Study investigators[5] showed that inhibition of tumor necrosis factor α with golimumab was as effective as other immunotherapies (including abatacept, alefacept, antithymocyte globulin, teplizumab, and rituximab) at preventing a rapid decline of C-peptide production (a surrogate of insulin secretion, which itself is

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

a surrogate of beta-cell mass) and an altered ratio of proinsulin to C-peptide (a loose measure of beta-cell stress), which herald stage 3 (overt diabetes).[6] They also detected slight improvements with respect to secondary end points, such as lower insulin requirements and a greater percentage of participants reaching glycated hemoglobin targets. It should not surprise us that immunomodulatory therapies that act on different stages of the autoimmune process, from the cellular (T and B lymphocytes) to the biochemical (cytokines) level, have similar effects; this similarity reflects the lack of more specific readouts of beta-cell number and cellular stress or death. Unlike other targets of autoimmune disease, the endocrine pancreas remains an inscrutable actor. Commonly used assays to detect incipient diabetes, including assays of autoantibodies as well as insulin and its coproducts proinsulin and C-peptide, do not capture the extent of beta-cell loss. At present, estimates of beta-cell loss and beta-cell regenerative potential are but an educated guess based on studies in animals.

Will combination treatments acting on complementary aspects of autoimmunity achieve superior results? Successful treatment of stage 3 disease (tertiary prevention) faces overwhelming odds, because beta cells are nearly depleted when symptoms arise. Earlier interventions and possibly better outcomes are hampered by the dearth of disease-activity markers and applicable methods for the imaging of endocrine islet cells. Currently, only teplizumab has been shown to delay the onset of the disease at stage 2 (secondary prevention)[7]; a broader application of this approach presents a challenge. Type 1 diabetes is relatively uncommon, even as its incidence is growing, especially in the adult- and late-onset variants.[8] Identifying persons at risk in the absence of a family history (primary prevention) is a tall order,[3] and even among those at risk, the timing of secondary prevention remains a judgment call. Furthermore, immunotherapy is not without risk (e.g., severe infection, immunosuppression, or lymphoma) and is logistically and emotionally fraught, as patients and their families struggle to cope with a new diagnosis of type 1 diabetes, a life-changing event. An example of the logistic hurdles surrounding immunotherapy can be seen in the T1GER study, which entailed a year-long regimen of golimumab. Even so, as regulators grapple with the implementation of immunotherapy in type 1 diabetes, providers should be educated as to which patients can benefit from this approach and to what extent.

We should also be mindful that this treatment debate is first-world centric. Current treatments for type 1 diabetes require resources not readily available in most parts of the world, where something as simple as refrigeration of insulin can become a logistic nightmare. While combinations of the approaches mentioned above, tailored to individual risk and potential benefits, are likely to make inroads in clinical practice, the need for a simpler, safer, and equally effective alternative to insulin remains.

References

1. Atkinson MA, Bluestone JA, Eisenbarth GS, et al. How does type 1 diabetes develop? The notion of homicide or β-cell suicide revisited. Diabetes 2011;60:1370–9. [PubMed: 21525508]
2. Warshauer JT, Bluestone JA, Anderson MS. New frontiers in the treatment of type 1 diabetes. Cell Metab 2020;31:46–61. [PubMed: 31839487]
3. Dayan CM, Korah M, Tatovic D, Bundy BN, Herold KC. Changing the landscape for type 1 diabetes: the first step to prevention. Lancet 2019;394:1286–96. [PubMed: 31533907]

4. Steffes MW, Sibley S, Jackson M, Thomas W. Beta-cell function and the development of diabetes-related complications in the Diabetes Control and Complications Trial. Diabetes Care 2003;26:832–6. [PubMed: 12610045]
5. Quattrin T, Haller MJ, Steck AK, et al. Golimumab and beta-cell function in youth with new-onset type 1 diabetes. N Engl J Med 2020;383:2007–17. [PubMed: 33207093]
6. Jacobsen L, Bundy B, Greco M, et al. Comparing beta cell preservation across clinical trials in recent-onset type 1 diabetes. Diabetes Technol Ther 2020 August 24 (Epub ahead of print).
7. Herold KC, Bundy BN, Long SA, et al. An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. N Engl J Med 2019;381:603–13. [PubMed: 31180194]
8. Mayer-Davis EJ, Lawrence JM, Dabelea D, et al. Incidence trends of type 1 and type 2 diabetes among youths, 2002–2012. N Engl J Med 2017;376:1419–29. [PubMed: 28402773]