Immunotherapy in Type 1 Diabetes: Emerging Therapies and Future Directions

Simran Thakkar,[1] Saptarshi Bhattacharya,[1] Lakshmi Nagendra,[2] Sanjay Kalra[3,4]

Abstract

Type 1 Diabetes Mellitus (T1D) is an autoimmune disorder marked by the destruction of insulin-producing pancreatic β-cells. While insulin therapy remains the standard of care, advancements in immunotherapy present promising alternatives aimed at halting disease progression and reducing insulin dependence. This brief review highlights key immunomodulatory therapies, including teplizumab, which has demonstrated the ability to delay the onset of T1D, and rituximab, known for preserving β-cell function, though its effects tend to be transient. Emerging treatments, such as stem-cell therapies, also show potential. However, significant challenges remain, including high costs, long-term safety concerns, and the need for personalized care. As this therapeutic landscape evolves, further research is critical to optimizing these strategies and moving closer to a potential cure for T1D.

Keywords: Type 1 diabetes mellitus, autoimmunity, immunotherapy, anti-CD3 monoclonal antibody, teplizumab,

DOI: https://doi.org/10.47391/JPMA.25-10

Introduction

Type 1 diabetes mellitus (T1D) is a complex autoimmune disorder characterized by the progressive destruction of insulin-producing pancreatic β-cells. While insulin therapy has been the cornerstone of T1D management for over a century, recent advancements in immunotherapy offer promising options that not only manage the disease but potentially halt its progression. This review explores the evolving landscape of immunomodulatory therapies including antibody-based therapies, antigen-specific strategies and stem-cell-based therapies, focussing on their potential to preserve β cell function.

[1]Department of Endocrinology, Indraprastha Apollo Hospitals, New Delhi, India [2]Department of Endocrinology, JSS Medical College, JSS Academy of Higher Education and Research, Mysore, India [3]Department of Endocrinology, Bharti Hospital, Karnal, Haryana, India [4]University Centre for Research & Development, Chandigarh University, Mohali, India

Correspondence: Dr Sanjay Kalra, **Email:** brideknl@gmail.com

ORCID ID. 0000-0003-1308-121

Stages of development of type 1 diabetes

The development of T1D progresses through three distinct stages. Stage 1 involves the presence of multiple autoantibodies while the individual remains euglycaemic. As the disease progresses to stage 2, dysglycaemia or impaired glucose tolerance emerges, indicating worsening β-cell function. By stage 3, the clinical onset of diabetes occurs, marked by significant β-cell destruction that leads to symptomatic hyperglycaemia and the need for insulin therapy.[1]

Pathogenesis of type 1 diabetes

The pathogenesis of T1D involves autoimmune destruction of β-cells of the pancreas by the activation of cytotoxic CD8+ T-cells, though the presence of autoantibodies suggests an additional role of B-lymphocytes. The initial step involves the presentation of antigens, including the insulin B-chain peptide (11-23) and other components of β-cell secretory granules, bound to major histocompatibility complexes I and II on antigen-presenting cells to CD4+ T-helper cells.[2] The activated CD4+ helper T-cells stimulate the effector cytotoxic CD8+ T-cell to destroy the islet β-cells. Regulatory T-cells counteract the autoreactive T-cells to maintain peripheral tolerance and immune homeostasis. An imbalance between the two leads to a breakdown of peripheral tolerance and eventually to the development of T1D.[3] The primary aim of immunotherapy in T1D is to prevent or at least delay the immune-mediated destruction of islet β-cells. Immunotherapy in T1D can be either–antibody-based therapy, antigen-based therapy, or stem cell therapy.

Teplizumab and Otelixizumab

Teplizumab is a humanized anti-CD3 monoclonal antibody that has demonstrated efficacy in delaying the onset of T1D in at-risk individuals. By binding to the CD3 receptor on T-lymphocytes, teplizumab alters T-cell signalling and can induce a state of T-cell tolerance. This intervention reduces the activation of autoreactive T-cells that destroy β cells. Teplizumab has been approved by FDA for use in adults and children over eight years with stage 2 T1D.[4]

The TrialNet study group demonstrated that teplizumab leads to sustained preservation of C-peptide response, indicative of retained β-cell function, paired with a

reduction in the incidence of clinical T1D.[5] These findings suggest that strategies focussed on modulating T-cell responses could transform disease management. However, teplizumab administration is accompanied by potential adverse events, including nausea, rash, and the possibility of cytokine release syndrome.[6]

Otelixizumab is another anti-CD3 monoclonal chimeric humanized antibody that has been evaluated in T1D, but did not demonstrate consistent improvement in C-peptide compared to placebo.[7,8]

Rituximab and other antibody-based therapies

Rituximab is also an antibody-based therapy, targeting CD20 on B-cells. Rituximab can preserve β-cell function in newly diagnosed T1D by reducing B-cell-mediated autoimmunity, leading to better glycaemic control and a requirement for lesser exogenous insulin. However, the effect of rituximab seems to be transient, with diminished efficacy beyond 12 months.[9] Combination therapies that may prolong the benefits observed with rituximab could be a possible solution to enhancing its efficacy.

A novel frontier, golimumab, TNFα monoclonal antibody, has demonstrated promising results in preserving β-cell function with favourable side effect profile in its phase 2 TIGER study.[10] Similarly, etanercept showed potential in pilot studies, though recent combinations with other agents like GAD-alum did not yield significant benefits.[11,12]

Alefacept and Abatacept

Alefacept and abatacept, both fusion proteins with distinct immune-modulating mechanisms, represent significant strides in targetting T-cell activation and proliferation. In the T1DAL trial, alefacept showed potential by decreasing exogenous insulin requirement and reducing hypoglycaemic events in newly diagnosed T1D, though efficacy waned after 12 months.[13] Abatacept, similarly, demonstrated promising preservation of β-cell function over two years and maintained benefits even after cessation of treatment, highlighting the long-term potential of costimulatory blockade.[14] Despite the demonstrated successes, challenges remain in translating these benefits into long-term disease modification across diverse patient populations.

Anti-thymocyte globulin

Anti-thymocyte globulin, has been used as a cost-effective immunotherapy to preserve the C-peptide response in recent onset T1D owing to its T-cell depleting properties and selective induction of the regulatory T-cells. However, higher doses were associated with significant adverse events like cytokine release syndrome.[15]

Antigen-based Immunotherapy

The antigen-specific approach involves the delivery of β-cell autoantigens through a route and regimen that induces immunological tolerance. Recent trials have focussed on the use of proinsulin and islet autoantigens to restore immune tolerance effectively.[16] Dual-peptide regimens combining different peptides have shown promise. However, challenges remain regarding the selection and delivery of suitable antigens, as well as patient-specific factors influencing treatment response.

Stem-cell based therapy

Embryonic stem cells (SCs), induced pluripotent SCs, and adult SCs have been explored for the management of T1D. Recent technological advances have enabled human clinical trials utilizing SC-derived pancreatic endoderm cells (PEC), paving the way for innovative approaches to treat T1D.

The newer PEC-Direct device, which involves subcutaneous implantation of PEC-01 cells within VC-02 devices, contains membrane openings that allow vascularization. This facilitates nutrient exchange and promotes the survival of the implanted cells. Though detectable levels of C-peptide in peripheral blood by 6-9 months post-transplant are observed, challenges such as graft loss and the requirement for long-term immunosuppression pose barriers to the widespread adoption of this strategy.[17]

Combination therapy and other approaches

Combination therapies have been attempted to address the multifactorial nature of autoimmune diabetes. Anti-interleukin 21 (anti-IL-21) antibody antagonizes IL-21 mediated autoreactive T-cell trafficking to pancreatic islets as well as the proliferation of effector and follicular helper T-cells. On the other hand, glucagon-like peptide-1 agonists like liraglutide have been reported to improve β-cell survival. The synergy observed with these treatments could pave the way for further exploration of combinatory approaches in future clinical trials.[18]

Janus kinase cytokine inhibitor, baricitinib, and tyrosine kinase inhibitor, imatinib, have shown significantly higher C-peptide response and reduced requirement of exogenous insulin with favourable side-effect profile.[19,20] Though promising, both require further research to establish long-term safety and efficacy, particularly in terms of optimal dosing and potential adverse effects.

Challenges and Considerations

Despite these promising developments, several

challenges remain. The cost of innovative therapies, such as teplizumab, raises concerns about accessibility and affordability. Thus, cost-effectiveness analysis should guide decision-making, ensuring that these therapies are not only effective but also feasible for widespread use.

Moreover, the long-term safety of immunomodulatory therapies must be scrutinized. While short-term benefits are often highlighted, the potential risks for unintended immune consequences or adverse events, such as cytokine release syndrome or viral infections could complicate the therapeutic landscape.

Conclusion

The landscape of T1D management is rapidly evolving with the advent of immunomodulatory therapies. These approaches offer the potential not only to manage hyperglycaemia more effectively but also to preserve or restore β-cell function. While current therapies such as teplizumab provide early intervention opportunities, challenges remain regarding patient selection, long-term safety, and cost-effectiveness. Future clinical trials should emphasize combining therapies and tailoring treatment to individual patients to maximize outcomes. A concerted effort towards understanding the immunological underpinnings of T1D will likely result in more effective therapies, moving us closer to a potential cure for this chronic disease.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

References

1. Insel RA, Dunne JL, Atkinson MA, Chiang JL, Dabelea D, Gottlieb PA, et al. Staging Presymptomatic Type 1 Diabetes: A Scientific Statement of JDRF, the Endocrine Society, and the American Diabetes Association. Diabetes Care. 2015;38:1964-1974. doi:10.2337/dc15-1419
2. Giwa AM, Ahmed R, Omidian Z, Majety N, Karakus KE, Omer SM, et al. Current understandings of the pathogenesis of type 1 diabetes: Genetics to environment. World J Diabetes. 2020;11:13-25. doi:10.4239/wjd.v11.i1.13
3. Pugliese A. Autoreactive T cells in type 1 diabetes. J Clin Invest. 2017;127:2881-2891 doi:10.1172/JCI94549
4. Carvalho T. FDA approves first drug to delay type 1 diabetes. Nat Med. 2023;29:280 doi:10.1038/d41591-022-00115-y
5. Herold KC, Bundy BN, Long SA, Bluestone JA, DiMeglio LA, Dufort MJ, et al. An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes. N Engl J Med. 2019;381:603-613. doi:10.1056/NEJMoa1902226
6. Kamrul-Hasan ABM, Mondal S, Nagendra L, Yadav A, Aalpona FTZ, Dutta D. Role of Teplizumab, a Humanized Anti-CD3 Monoclonal Antibody, in Managing Newly Diagnosed Type 1 Diabetes: An Updated Systematic Review and Meta-Analysis. Endocr Pract Off J Am Coll Endocrinol Am Assoc Clin Endocrinol. 2024;30:431-440. doi:10.1016/j.eprac.2024.03.006
7. Aronson R, Gottlieb PA, Christiansen JS, Donner TW, Bosi E, Bode BW, et al. Low-dose otelixizumab anti-CD3 monoclonal antibody DEFEND-1 study: Results of the randomized phase III study in recent-onset human type 1 diabetes. Diabetes Care. 2014;37:2746-2754 doi:10.2337/dc13-0327
8. Ambery P, Donner TW, Biswas N, Donaldson J, Parkin J, Dayan CM. Efficacy and safety of low-dose otelixizumab anti-CD3 monoclonal antibody in preserving C-peptide secretion in adolescent type 1 diabetes: DEFEND-2, a randomized, placebo-controlled, double-blind, multi-centre study. Diabet Med. 2014;31. doi:10.1111/dme.12361
9. Pescovitz MD, Greenbaum CJ, Bundy B, Becker DJ, Gitelman SE, Goland R, et al. B-lymphocyte depletion with rituximab and β-cell function: Two-year results. Diabetes Care. 2014;37:453-459. doi:10.2337/dc13-0626
10. Quattrin T, Haller MJ, Steck AK, Felner EI, Li Y, Xia Y, et al. Golimumab and Beta-Cell Function in Youth with New-Onset Type 1 Diabetes. N Engl J Med. 2020;383:2007-2017 doi:10.1056/nejmoa2006136
11. Mastrandrea L, Yu J, Behrens T,Buchlis J, Albini C, Fourtner S, et al. Etanercept treatment in children with new-onset type 1 diabetes: Pilot randomized, placebo-controlled, double-blind study. Diabetes Care. 2009;32.1244-1249. doi:10.2337/dc09-0054
12. Ludvigsson J, Routray I, Vigård T,Hanas R,Rathsman B, Carlsson A, et al. Combined Etanercept, GAD-alum and vitamin D treatment: an open pilot trial to preserve beta cell function in recent onset type 1 diabetes. Diabetes Metab Res Rev. 2021;37:e-3440. doi:10.1002/dmrr.3440
13. Rigby MR, DiMeglio LA, Rendell MS, Felner EI, Dostou JM, Gitelman SE, et al. Targeting of memory T cells with alefacept in new-onset type 1 diabetes (T1DAL study): 12 month results of a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Diabetes Endocrinol. 2013;1:284-294.. doi:10.1016/S2213-8587(13)70111-6
14. Orban T, Bundy B, Becker DJ, DiMeglio LA, Gitelman SE, Goland Ret al. Co-stimulation modulation with abatacept in patients with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled trial. The Lancet. 2011;378:412-419. doi:10.1016/S0140-6736(11)60886-6
15. Gitelman SE, Gottlieb PA, Rigby MR, Felner EI, Willi SM, Fisher LK,et al. Antithymocyte globulin treatment for patients with recent-onset type 1 diabetes: 12-month results of a randomised, placebo-controlled, phase 2 trial. Lancet Diabetes Endocrinol. 2013;1:306-3016 doi:10.1016/S2213-8587(13)70065-2
16. So M, Elso CM, Tresoldi E, Pakusch M, Pathiraja V, Wentworth JM, et al. Proinsulin C-peptide is an autoantigen in people with type 1 diabetes. Proc Natl Acad Sci U S A. 2018;115:10732-10737. doi:10.1073/pnas.1809208115
17. Hogrebe NJ, Ishahak M, Millman JR. Developments in stem cell-derived islet replacement therapy for treating type 1 diabetes. Cell Stem Cell. 2023;30:530-548. doi:10.1016/j.stem.2023.04.002
18. von Herrath M, Bain SC, Bode B, Clausen JO, Coppieters K, Gaysina L, et al. Anti-interleukin-21 antibody and liraglutide for the preservation of β-cell function in adults with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Diabetes Endocrinol. 2021;9:212-224. doi:10.1016/S2213-8587(21)00019-X
19. Waibel M, Wentworth JM, So M, Couper JJ, Cameron FJ, MacIsaac RJet al. Baricitinib and β-Cell Function in Patients with New-Onset Type 1 Diabetes. N Engl J Med. 2023;389:2140-2150. doi:10.1056/nejmoa2306691
20. Gitelman SE, Bundy BN, Ferrannini E, Lim N, Blanchfield JL, DiMeglio LA, et al. Imatinib therapy for patients with recent-onset type 1 diabetes: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Diabetes Endocrinol. 2021;9:502-514. doi:10.1016/S2213-8587(21)00139-X