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IMMUNOPATHOGENESIS AND EMERGING IMMUNOTHERAPIES IN TYPE 1 DIABETES MELLITUS: THE ROLE OF TEPLIZUMAB IN DISEASE MODULATION

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Abstract: Type 1 diabetes mellitus (T1DM), a complex chronic disease with an intricate etiology and pathogenesis, involves the recognition of self-antigens by pancreatic islet autoantigen-specific T cells and plays crucial roles in both early and late-stage destruction of beta cells, thus impacting disease progression. Antigen-specific T cells regulate and execute immune responses by recognizing antigens, playing broad roles in treating various diseases. Immunotherapy targeting antigen-specific T cells holds promising potential as a targeted treatment approach**.**
Aim of the study: This review outlines the pathogenesis of diabetes, emphasizing the pivotal role of pancreatic islet autoantigen-specific T cells in the progression and treatment of T1DM. Exploring this avenue in research holds promise for identifying novel therapeutic targets for effectively managing diabetes.
Materials and methods: This review is a comprehensive search of PUBMED from 2015 to 2025.
Conclusion: Type 1 diabetes is a chronic autoimmune ailment that requires a tremendous amount of medical care and lifelong follow-ups that can often become burdensome to the finances of the patients. Advancements in patient care and better treatment modalities can benefit the patient and decrease the burden on healthcare facilities. Immunotherapy is a promising approach to provide better care to such patients.

Keywords: Type 1 diabetes; Management; Immunotherapy; Pathogenesis; Autoimmune disease; Teplizumab

INTRODUCTION

According to the WHO, Type 1 diabetes mellitus (also known previously as juvenile diabetes) is an autoimmune endocrine disorder that results from deficient production of insulin by the pancreatic beta cells. This deficiency necessitates the daily administration of insulin to fulfill the body's requirements. About 9 million people, mostly from high-income countries, were afflicted, in 2017.[1] Most often diagnosed in children and young adults, who develop symptoms over a short period. The incidence peak of the disease is 10-14 years of age.[2] T1DM patients exhibit symptoms like those of Type 2 DM: polydipsia, polyuria, polyphagia, fatigue, and delayed wound healing. In addition to this, there might be unexplained weight loss. Stages of T1DM can be described by the following criteria: [3]

Table 1: The criteria and stages of T1DM.

CRITERIA	STAGE 1	STAGE 2	STAGE 3

β-cell autoimmunity (with the presence of autoantibodies)	Present	Present	Present
β-cell loss	Present	Present	Present
Dysglycaemia	Absent	Hyperglycemia	Hyperglycemia
Symptoms	Absent	Absent	Present

A common complication of T1DM is diabetes ketoacidosis (DKA). Characterized by vomiting, abdominal pain, dyspnea, polyuria, fatigue, mental confusion, and loss of consciousness, the onset is rapid. [4] DKA is triggered by infection, improper insulin administration, stroke, trauma, alcohol or drug use, or medication such as diuretics or corticosteroids.[5]

PATHOGENESIS

The destruction of the Beta cell of the pancreas is the chief cause of T1DM. This loss of beta cell population leads to a state of deficient insulin production, consequently leading to elevated blood glucose levels in the body. According to Katsarou et al, while the etiology is not completely understood, the pathogenesis involves T-cell-mediated obliteration of beta cells. Interactions between T cells and B cells lead to islet–targeting autoantibody formation. While the initial trigger remains unidentified, the emergence of the first antibody targeting pancreatic islets indicates that dendritic cells presented islet components as antigens, which then activated specific CD4+ and CD8+ T cells to initiate an autoimmune response. Additionally, there is evidence of CD4+ and CD8+ T-cells which are specific for beta cell autoantigens in patients ranging from early stage to stage 3 T1DM. [6] In a histopathological examination of insulitis/immune-infiltrated islets, CD8+ T cells are present in the majority vis-à-vis CD4+ T cells.[7] These insulitis studies, though common in animal models depicting type 1 diabetes, are variable and rare in human models.[8]

The initial antibodies that are developed against insulin or protein GAD65, followed by antibodies against proteins IA-2, IA-2β, and/or ZNT8. Given the autoimmune nature of the disease, it can be defined by the presence of any of the autoantibodies. [6] The polygenetic nature of T1DM corresponds to a risk of development of 30-70% in identical twin studies; to a risk of 6-7% in siblings, and a risk of 1-9% in the case of a diabetic parent.[9] The development of the disease is also strongly linked to specific genes within the HLA complex, particularly the DQA and DQB genes. The HLA-DR/DQ alleles can either be predisposing in nature or protective. [10]

The environmental factors leading to the predisposition of the disease are poorly defined but still believed to be of consequence in the pathogenesis of the disease. The American Diabetes Association (ADA) recommends screening type 1 diabetes patients for thyroid disorders such as Hashimoto's or Graves disease, along with celiac disease. These patients also present with an increased risk for the development of primary adrenal insufficiency, autoimmune gastritis, autoimmune hepatitis, and myasthenia gravis. [11] Norris et al also appraise other factors such as higher maternal age, pre- and early gestational obesity, childhood obesity, vitamin D and omega-3 fatty acid deficiency, along with high dietary sugar intake.[12]

DIAGNOSIS OF TYPE 1 DIABETES MELLITUS

According to the American Diabetes Association, diabetes can be diagnosed based on fasting blood glucose concentration of above 7·0 mmol/L (126 mg/dL), a random blood glucose concentration above 11·1 mmol/L (200 mg/dL) with symptoms, or an abnormal result from an oral glucose tolerance test.[9] There are additional recommendations for diagnosis of diabetes for anyone exhibiting hyperglycaemia or random blood glucose levels 11.1 mmol/L, or glycated haemoglobin (haemoglobin A1C) levels at or above 48 mmol/mol (6.5%). But as dysglycemia can progress rapidly in T1DM patients, HbA_{1c} is not as sensitive as fasting or stimulated blood glucose measurements for diagnostic purposes. [13]

After the establishment of the diabetes diagnosis, it is essential to differentiate between T1DM and Type 2 Diabetes Mellitus. C-peptide is a by-product of insulin release and thus is a quantitative indicator of endogenous insulin. It is not affected by therapeutic insulin replacement, and very low levels are usually indicative of type 1 diabetes. [14] While measuring low C-peptide levels can help classify diabetes and guide treatment for patients examined more than three years after diagnosis, as it indicates a significant lack of self-produced insulin, no single

symptom or sign can definitively differentiate type 1 from other types of diabetes when diagnosis is first made.[9] Butler et al recommend that the differing clinical presentation can help to distinguish between the two.[14]

Table 2: Clinical features of diabetes mellitus.

Clinical Features	Type 1 Diabetes Mellitus	Type 2 Diabetes Mellitus
Weight loss	Yes	Unusual
Ketonuria	Yes	No, unless the patient was recently fasting
Time course of symptoms	Weeks or days	Months to years
Severity of symptoms	Often marked	Variable, but usually not severe
Family history	Possible family history of autoimmune disease and/or insulin dependence at a young age	Family history present in 30% with onset in adult life
Age	Peak age in pre-school and teenage years, but can present at any age	Typically, after the age of 40, but can present in younger patients

Butler et al also state that differentiating type 1 from type 2 can be difficult in:[14]

- Patients under 40 who are initially treated with insulin but clinically appear to have type 2 diabetes
- Patients 40 and older with late-onset diabetes who require insulin and share characteristics of patients with type 1 diabetes, such as a BMI <25 kg/m^2

The first line testing in patients with no acute symptoms consists of anti-glutamic acid decarboxylase (anti-GAD) (highest diagnostic sensitivity in adult-onset type 1 diabetes),19 islet cell cytoplasmic autoantibodies (ICA), and insulin autoantibodies (IAA). [14]

Table 3: Autoantibody, target and specificity for diabetes.

Autoantibody	Target	Specificity
Anti-glutamic acid decarboxylase autoantibodies (Anti-GAD)	Antibodies against a specific enzyme present in pancreatic β cells	Present in 84% of patients with type 1 diabetes
Insulin autoantibodies (IAA)	Antibodies targeted against the insulin molecule	Presence is dependent on age and sex **Age**: under 10 years- 81%, older- 61% **Sex**: under 15 years, M=F Over 15 years, M: F=2:1
Insulinoma-associated-2 autoantibodies (IA-2)	Antibodies mounted against a specific enzyme in β cells	Present in 58% of patients with type 1 diabetes
Islet cell cytoplasmic autoantibodies (ICA)	Reaction between human islet cell antibodies and islet cell proteins from animal pancreas	Present in 70-80% of new onset patients with type 1 diabetes
Zinc transporter 8 autoantibodies (ZnT8Ab)	Antibodies targeting a β cell specific enzyme	Present in 80% of patients with type 1 diabetes, with 99% specificity

IMMUNOTHERAPEUTIC MANAGEMENT OF TYPE 1 DIABETES

While conventional therapy modalities such as insulin supplementation have been the management mainstay, along with the use of drugs such as metformin, glucagon-like peptide-1(GLP-1) receptor agonists, dipeptidyl peptidase-4 inhibitors, and sodium-glucose co-transporter-2 (SGLT2) inhibitors.[9] In type 1 patients with insulin resistance, metformin is used as a sensitizer, but is not as effective in patients under 18 years of age or those with obesity. [15] SGLT2 inhibitors primarily act on the kidneys and inhibit the reabsorption of glucose and increasing urinary excretion of glucose. They are also beneficial in improving lipid profiles and in weight reduction. GLP-1 agonists stimulate insulin production while inhibiting apoptosis of pancreatic beta cells.[16] Glucagon replacement

therapy has also had a resurgence with nasal formulations for emergencies, and stable liquid formulation for closed-loop systems along with insulin. [9]

The autoimmune pathogenesis of T1DM provides the avenue for immune interventional therapies. The immunological therapies aim to treat T1DM beyond the symptomatic relief provided by insulin and other conventional modalities, with the development of immunotherapy targeting islet-specific immune pathways.[17]

1. Non-specific immunosuppressants

Immunosuppressive agents such as cyclosporin, azathioprine with prednisone, and methotrexate were the subjects of the earliest immunotherapy regimen for T1DM. Cyclosporin provided remission with preservation of beta cell function, but it was short-lived, and higher doses required for remission were responsible for nephrotoxicity, higher incidences of infection, and recurrence of the disease after the cessation of treatment. [18]

Other agents, such as methotrexate, were ineffective, or like azathioprine and prednisolone in both mono- and combination therapy, showed some delay in progression of T1DM but on a long term basis would lead to toxicities and recurrence on withdrawal, leading to diminished preference for these drugs.[18]

2. Beta-cell replacement

With either allogenic solid organ pancreas or islet transplantation for beta cell replacement has shown some promising results have been shown in the reversal of T1DM, but it necessitates the lifelong use of immunosuppressive drugs to prevent graft rejection. The immunosuppressive regimen previously followed was based on ATG induction immunosuppression followed by long-term cyclosporine A, steroids, and azathioprine; however, only a small percentage of patients managed to remain insulin-free. With the replacement of the regimen with the Edmonton protocol, which was free of corticosteroids, using daclizumab for induction, sirolimus, and low-dose tacrolimus for maintenance of the immunosuppression. Considering the long-term risks associated with chronic immunosuppression, currently, ADA recommends islet transplantation for individuals simultaneously undergoing renal transplantation, have already received a renal transplantation, or have recurrent ketoacidosis or severe hypoglycemia despite intensive glycemic management should undergo transplantation. [17]

3. Cytokine therapies

Cytokines play a pivotal role in mediating the pathogenesis of T1D. Inflammatory cytokines such as TNF, IL-6, and IL-1 contribute to the progression of the disease, which is contradicted by the protective function of regulatory cytokines such as IL-33 and TGF-ß. IL-1 inhibitors such as anakinra and canakinumab antagonise the direct β-cell proapoptotic action of interleukin-1β. [18]

4. Anti-CD3 therapies

As the activation of T cells play a chief role in the pathogenesis T1DM, there are promising avenues in terms of interventions targeting the activation of T-cells. One such intervention aims at CD3 with anti-CD3 monoclonal antibodies. These drugs are hypothesised to work by direct inactivation of T-cells, inhibition of apoptosis induction, and induction of apoptosis of activated T cells. [18]

An anti-CD3 monoclonal antibody, Otelixizumab, which has limited Fc receptor binding, was beneficial in preserving beta-cell function at higher doses but precipitated adverse effects that ranged from cytokine release syndrome, Epstein-Barr virus reactivation, and cytomegalovirus infection, while failing to show appreciable differences in C-peptide and HBA_{1C} levels. [18]

Teplizumab [hOKT3γ (Ala-Ala)] is a drug that has been developed that is representative of a modified humanized form of the antibody that has a mutated human Fc receptor, which resulted in a decrease in T cell activation along with immunogenicity.[17]. Teplizumab has a high affinity for binding to the ε chain of CD3. The two Leu→Ala substitutions in the OKT3 molecule in the Fc region reduced the Fc-receptor binding, consequently decreasing T-cell activation, T-cell proliferation, and cytokine release in human peripheral blood mononuclear cell cultures by 100- to 1000- times. [19]

Teplizumab partially agonises the effect of CD8+ T cells, which is integral to the beta cell destruction by the autoimmune response of the body.[20][21] The drug did not require continuous administration.[18] In the clinical trial of the drug, a single course could preserve C-peptide levels along with reduced insulin requirements and HBA_{1C} levels for approximately 24 months. [22] In extension studies, its effect continued for up to 5 years, along with an increase in the partially exhausted memory $KLRG1^{+}TIGIT^{+}CD8^{+}$ T cells, along with a decrease secretion of IFNγ and TNFα. [23]

Analogous to other immunotherapies, the outcome of the intervention with Teplizumab is affected by the stages and beta-cell reserve at the initiation of treatment. A more favourable outcome was observed if the treatment was administered soon after or before diagnosis at stage 3, along with better C-peptide response in younger patients.[18]

Teplizumab has relatively mild adverse effects- self-limited lymphopenia, skin and subcutaneous disease, GI symptoms [24], which was reiterated by Alves et al. [25]

Considering preclinical studies and multiple clinical trials of both stage 2 and Stage 3 T1DM patients [22,26], Teplizumab received FDA approval in 2022 to delay the progression in adults to stage 3 T1DM and in children ≥8 years old with stage 2 disease. Teplizumab became the first therapeutic agent proven for delayed onset of an autoimmune condition. [27] Salame et al observed an overall positive outcome of immunotherapy in patients, both children and young adults with high C-peptide levels, lowered HBA_{1C} levels, along with reduced requirements for insulin.[28] O'Donnell et al observed high favourability of the medicine among the patients and the caregivers of patients who were prescribed teplizumab, with an improvement in their conditions.[29] Teplizumab was also investigated for use in the treatment of other conditions such as acute transplant rejection and psoriatic arthritis. [19]

CONCLUSION

Type 1 diabetes is a chronic autoimmune ailment that requires a tremendous amount of medical care and lifelong follow-ups that can often become burdensome to the finances of the patients. Advancements in patient care and better treatment modalities can benefit the patient and decrease the burden on healthcare facilities. Immunotherapy is a promising approach to provide better care to such patients.

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The first author drafted the original text of manuscript. A final consent from each author is required before the material is submitted to a journal for publication. Each co-author made contributions to the creation of the table and figures, the literature review, and the manuscript's editing.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ETHICAL APPROVAL

Not Applicable

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