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Diplôme d'État de Docteur en Pharmacie

NOUVELLES PERSPECTIVES DANS LA PRISE EN CHARGE DU DIABETE DE TYPE 1 : REVUE DE LITTERATURE SUR LA PREVENTION, LE DEPISTAGE ET LES INNOVATIONS MEDICAMENTEUSES

NEW PERSPECTIVES IN THE CARE OF TYPE 1 DIABETES: A LITERATURE REVIEW OF PREVENTION, SCREENING AND PHARMACEUTICAL INNOVATIONS

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Plan

Liste des abréviations

ACD/DKA	Acidocétose Diabétique / *Diabetic Ketoacidosis*
ADA	Association Américaine du Diabète / *American Diabetes Association*
AGT	*Abnormal Glucose Tolerance*
ASC/AUC	Aire Sous la Courbe */ Area Under the Curve*
ATG	*Anti-Thymocyte Globulin*
CD	*Cluster of Differentiation*
CGM	*Continuous Glucose Monitoring*
CTLA4Ig	*Cytotoxic T-Lymphocyte-Associated 4 protein Immunoglobulin*
DCCT	*Diabetes Control Complications Trial*
DT1 / T1D	Diabète de Type 1 */ Type 1 Diabetes*
GAD	*Glutamic Acid Decarboxylase*
GAD-alum	*Recombinant human GAD65 in alum*
GCSF	*Granulocyte Colony-Stimulating Factor*
HbA1c	*Hémoglobine glyquée / Glycated hemoglobin*
HLA	*Human Leukocyte Antigen*
IA-2	*Islet Antigen 2*
IAA	*Insulin Antoantibodies*
IFN	*Interferon*
IL	*Interleukin*
JAK	*Janus Kinase*
mAb	*Monoclonal Antibody*
MMTT	*Mixed-Meal Tolerance Test*
NOD	*Non Obese Diabetic*
PD1	*Programmed cell Death protein 1*
R	*Receptor*
STAT	*Signal Transducer and Activator of Transcription*
T cell	*T Lymphocyt*
TH	*T-cell Helper*
TNF	*Tumor Necrosis Factor*
TXNIP	*Thioredoxin-Interacting Protein*
ZnT8	*Zinc Transporter 8*

Introduction

1. Contexte de la réalisation

1.1. Le contexte du diabète de type 1

Le diabète de type 1 (DT1) est une maladie chronique auto-immune caractérisée par la destruction des cellules bêta pancréatiques productrices d'insuline. Un événement déclencheur initie une réponse auto-immune dans le pancréas. Les lymphocytes T auto-réactifs sont alors activés, infiltrent les îlots pancréatiques et attaquent les cellules bêta. Ces dernières sont progressivement endommagées ou détruites. Ce dysfonctionnement des cellules bêta médié par le système immunitaire entraîne une déficience en production d'insuline et une dérégulation de la glycémie. Le DT1 se développe de manière cliniquement silencieuse sur une période de quelques mois à plusieurs années. Sa progression est caractérisée en 3 stades et définie par des paramètres clés qui apparaissent après l'initiation de l'auto-immunité. Le stade 1 du DT1 se caractérise par la présence d'au moins deux auto-anticorps. Le stade 2 est défini par la présence d'au moins deux auto-anticorps associée à un dysfonctionnement des cellules β, dont la destruction progressive entraîne une dysglycémie. Enfin, le stade 3 correspond à la phase clinique du diabète de type 1, caractérisée par une hyperglycémie. (1) De nombreux patients vivant avec un DT1 présentent des complications allant du déséquilibre glycémique aigu (acidocétose diabétique (ACD), hypoglycémie sévère) aux atteintes vasculaires chroniques, favorisant les maladies cardiovasculaires, la néphropathie, la neuropathie et la rétinopathie. (2)

1.1.1. L'incidence du diabète de type 1 augmente

La prévalence et l'incidence du DT1 sont en augmentation constante en France et à l'échelle mondiale.

L'incidence correspond au nombre de nouveaux cas d'une maladie dans une population sur une période donnée, tandis que la prévalence représente le nombre total de personnes atteintes d'une maladie dans une population à un moment donné.

Au cours du XXème siècle en Europe et en Amérique du Nord, une augmentation de l'incidence du DT1 d'environ 2 à 3 % par an a été rapportée. (3) Cela suggère une influence probable de facteurs environnementaux et/ou comportementaux dans le développement de la maladie. Une étude portant sur 84 000 enfants dans 22 pays européens, menée entre 1989 et 2013, a révélé que les taux d'incidence continuent

d'augmenter dans tous les groupes d'âge de l'enfance, bien que dans les pays à risque élevé (comme la Finlande et la Norvège), cette augmentation semble se stabiliser. (3) En 2021, on estimait à 8,4 millions le nombre de personnes vivant avec le DT1 dans le monde. (1,4) Cette année-là, environ 510 000 de nouveaux cas ont été diagnostiqués (âge médian de début de la maladie : 29 ans), et environ 35 000 personnes non diagnostiquées sont décédées dans les 12 mois suivant l'apparition des symptômes. (4) Aux États-Unis, les prévisions actuelles estiment que l'incidence du DT1 chez les moins de 20 ans augmentera de 23 % d'ici 2050. (3) Cependant, *Gregory et al.* ont présenté 2 scénarios dont les chiffres sont bien plus inquiétants. En effet, dans son premier scénario, (4) *the conservative estimate* (l'estimation prudente), le nombre de personnes vivant avec un DT1 augmentera de 66 % dans le monde entre 2020 et 2040, passant de 8,11 (7,82–8,42) millions à 13,51 (12,65–14,42) millions. Le changement le plus important se produira chez les personnes âgées de 20 ans et plus. Dans le deuxième scénario de *Gregory et al*, *the momentum estimate* (l'estimation de l'impulsion), la prévalence augmentera de 116 % dans le monde entre 2020 et 2040, passant de 8,11 (7,82–8,42) millions à 17,43 (15,63–19,39) millions. (4)

1.2. Les défis à relever dans la prise en charge

1.2.1. Les limites des traitements actuels

Aujourd'hui le traitement standard repose sur l'administration d'insuline de manière journalière, ce qui implique des injections multiples quotidiennes ou le port d'une pompe à insuline, ainsi qu'un contrôle fréquent de la glycémie grâce à des capteurs ou à des tests de glycémie capillaire. Un ajustement constant des doses en fonction de l'alimentation et de l'activité physique est nécessaire. Toutes ces contraintes peuvent avoir un impact significatif sur la qualité de vie des patients et de leur famille. (5)

1.2.2. La nécessité d'explorer de nouvelles approches thérapeutiques pour une prise en charge plus efficace

De plus, la gestion de l'insulinothérapie est délicate car un surdosage peut provoquer des hypoglycémies potentiellement dangereuses, pouvant aller jusqu'au coma diabétique, tandis qu'un dosage insuffisant peut mener à des hyperglycémies voire des acidocétoses potentiellement mortelles. Il peut être difficile d'atteindre l'équilibre glycémique optimal, et certains patients n'arrivent pas à le maintenir. En effet, seulement 17 % des patients âgés de moins de 18 ans, (6) 22 % des enfants âgés de 6 à 12 ans et 17 % des enfants âgés de 13 à 17 ans (7) ont atteint l'objectif

d’hémoglobine glyquée (HbA1c) de l'Association Américaine du Diabète (ADA) de <7,5 %. (8)

Malgré les traitements disponibles aujourd’hui, le contrôle insuffisant du DT1 auto-immun est associé à des complications microvasculaires et macrovasculaires à long terme, pouvant affecter divers organes comme les yeux, les reins, le cerveau et le cœur. (9)

En plus des effets physiques du DT1, les personnes vivant avec cette maladie doivent également faire face à une charge mentale considérable. Cette pression psychologique peut avoir des répercussions sur leur capacité à travailler efficacement, altérer leur qualité de vie au quotidien, et impacter leurs relations familiales. (10) La gestion constante de la maladie, les inquiétudes liées à la santé, notamment la peur de l’hypoglycémie (10), peuvent également engendrer un stress supplémentaire pour leurs proches. La détresse liée au diabète est fréquente chez les familles de patients diabétiques. (11)

2. Objectif de la thèse

L’objectif de cette thèse est d’étudier les nouveautés de prise en charge dans le cadre du DT1, et plus spécifiquement sur les innovations dans le dépistage précoce, les stratégies de prévention et l’identification de nouvelles cibles thérapeutiques.

New perspectives in the care of Type 1 Diabetes: A literature review of prevention, screening and pharmaceutical innovations

1. Introduction

Type 1 diabetes (T1D) is an autoimmune disease that leads to the destruction of pancreatic islet β-cells, resulting in metabolic failure requiring lifelong insulin therapy. T1D primarily affects individuals with a genetic predisposition, (1) although not all cases exhibit this genetic factor. The onset and progression of the disease are often triggered by environmental such as viral infections, with Coxsackie B virus, but also dietary and hygiene factors, (3) and immunological factors. While the involvement of multiple factors may suggest that T1D is rare, it is actually not uncommon. (1)

In 2021, there were an estimated 8.4 million people worldwide living with T1D, with around 510,000 new cases diagnosed in that year. (1,4) Approximately 35,000 non-diagnosed individuals died within 12 months of symptom onset. (4) The annual rise in incidence (+2.8% worldwide, +3.4% in Europe) could double the disease prevalence by 2040. In France, the incidence rate assessed by Santé Publique France was 17.2/100.000 between 2015 and 2017. If this is an intermediate global incidence, the annual increase is estimated at 4%. (12) In the United States, current forecasts estimate that the incidence of T1D in the under-20s will rise by 23% by 2050. (3) T1D represents a significant concern in population health.

T1D progresses quietly over the course of several months to years. Its development is marked by specific indicators that appear after the onset of autoimmunity. In fact, T1D involves several stages, each with its own specific features. Stage 1 is characterized by the presence of two or more autoantibodies, stage 2 is defined by two or more autoantibodies and β-cell dysfunction, as β-cell mass is progressively eliminated and this is associated with a dysglycemia, and stage 3 equates to clinical T1D with hyperglycemia. (1) The risk of developing clinical T1D is not the same depending on the stage the diabetic patient is at. Individuals diagnosed as stage 1 have a 35–50% risk of progressing to clinical T1D within 5–6 years. This risk is raised to 75% for those at stage 2, with a median time to diagnosis of 2 years. (13)

T1D has a profound impact on patients' overall health and quality of life, with clinical implications that extend beyond blood sugar management. (9) It affects physical, emotional, and social well-being often leading to life-threatening complications. Diabetic ketoacidosis (DKA), a severe metabolic disturbance that requires immediate medical

intervention to prevent serious complications or even death, (3) arises when there is an absolute deficiency of insulin. In France, 58% of deaths in people with T1D aged between 1 and 14 years are linked to DKA ; (14) 70% of these DKA deaths involve children aged between 1 and 4 years. (14) Cardiovascular diseases, such as coronary heart disease or heart attack significantly reduce life expectancy, particularly in those diagnosed at a young age, according to the Swedish National Diabetes Registry. (12) Neuropathies, reported in up to 90% of diabetic patients, leads to pain, disability, and psychological effects. (15) Diabetic retinopathy is a highly specific neurovascular complication of T1D, with prevalence strongly related to both the level of glycemic control and the duration of diabetes. (16) Retinopathy most commonly occurs after the onset of puberty and after 5–10 years of diabetes duration (17) and can cause blindness. Diabetic kidney disease or diabetic nephropathy is another common microvascular diabetic complication where it has been estimated to be prevalent in 30% of T1D patients. (18,19) Adolescents with T1D are 2.3 times more likely to suffer from anxiety and depression compared to their healthy peers. (5,11) Data from the Diabetes Control and Complications Trial (DCCT) has established that maintaining a glycated hemoglobin (HbA1C) <7% substantially reduces the occurrence of microvascular and macrovascular complications of T1D. (3) Only 17% of patients under 18 years old achieved the *American Diabetes Association* (ADA) recommended HbA1c goal of <7.5% (58 mmol/mol), and no improvement was observed as they got older. (6)

Therefore, despite recent advances with new technologies (insulin pump, closed loop, continuous glucose monitoring (CGM)) the current standard of care (ie: insulin therapy) doesn't enable an optimal glycemic control and patients with T1D face a wide range of short and long-term complications. (20)

Consequently, there is an urgent need to discover new approaches to support individuals living with T1D and prevent complications and hospitalization. The ability to diagnose T1D at presymptomatic stages enables the physicians to act before the progression to stage 3 and the initiation of insulin therapy, helping to preserve a significant β-cell mass. Investigations have provided strong evidence that the preservation of residual β-cell function after the diagnosis of T1D decreases the need for exogenous insulin and is associated with protection from vascular complications and severe hypoglycemia. (21,22)

This review aims to answer the following question: What are the current and future strategies for managing T1D focusing on prevention, early detection, and emerging therapeutic targets (including immunotherapies)? Early diagnosis of T1D through screening is associated with a lower incidence of DKA (from 25-62% to 4-6%) at clinical onset. (12,23) After these findings, the results of the TrialNet study, published online

in the *New England Journal of Medicine* in June 2019 (24), provided the first evidence that clinical T1D can be delayed with immunotherapy. (24,25) This represents a real change in patient care.

The aim of this literature review was to identify major developments and recent advances in the management of T1D, in terms of screening, diagnosis and targets for innovative therapies. The focus was primarily on immunotherapies, with a single exception, rather than technological approaches.

2. Methods

2.1. Literature search strategy

This analysis was conducted through an in-depth review of the scientific literature, covering the period from 2015, to beginning of 2025, with the aim of highlighting recent advances in pharmacology. The primary database used for the search is PubMed, supplemented by 'ClinicalTrial.gov' to identify companies-sponsored clinical trials. A manual detailed analysis of the references cited in the articles was carried out, by completing the bibliography produced by the author on the theme and reviewing recent issues of the main journals that had published on the subject to identify articles and book chapters which, despite their interest, had not been identified electronically.

2.2. Inclusion and exclusion criteria

The selection criteria for this review were as follows: 1/ articles published between January 1, 2015, and February 15, 2025; 2/ theoretical or empirical studies of recognized quality, including publications in peer-reviewed journals with an impact factor above 2 (with exceptions); 3/ relevance to the research theme; and 4/ availability in French or English. Included study types comprised books and documents, clinical studies, clinical trials (Phase II, III, IV), meta-analyses, multicenter studies, observational studies, randomized controlled trials, reviews, and systematic reviews. Selection was also based on key words, such as T1D, immunotherapies, screening, beta-cell preservation, autoantibodies, the therapies studied, psychological complications related to T1D, and both chronic and acute complications. Methodological quality was assessed, considering experimental robustness, sample sizes, and bias management.

2.3. Screening

The entire screening process was done by a reviewer (C Blanc). No external validation of the analysis was performed. Studies were screened by reading the title and abstract for inclusion criteria or exclusion criteria. A second round of screening was further completed by reading the full text of the article.

An analysis table was used to conduct an ordered reading of the articles, highlighting the information contained in each article, the study methodologies, the main results encountered, and the main avenues for future research.

3. Results

3.1. Literature search results

A total of 3,561 articles were retrieved. After title screening, 157 articles were selected for full-text review, of which 79 were excluded. An additional 36 studies were manually added, resulting in 57 articles included in the final document.

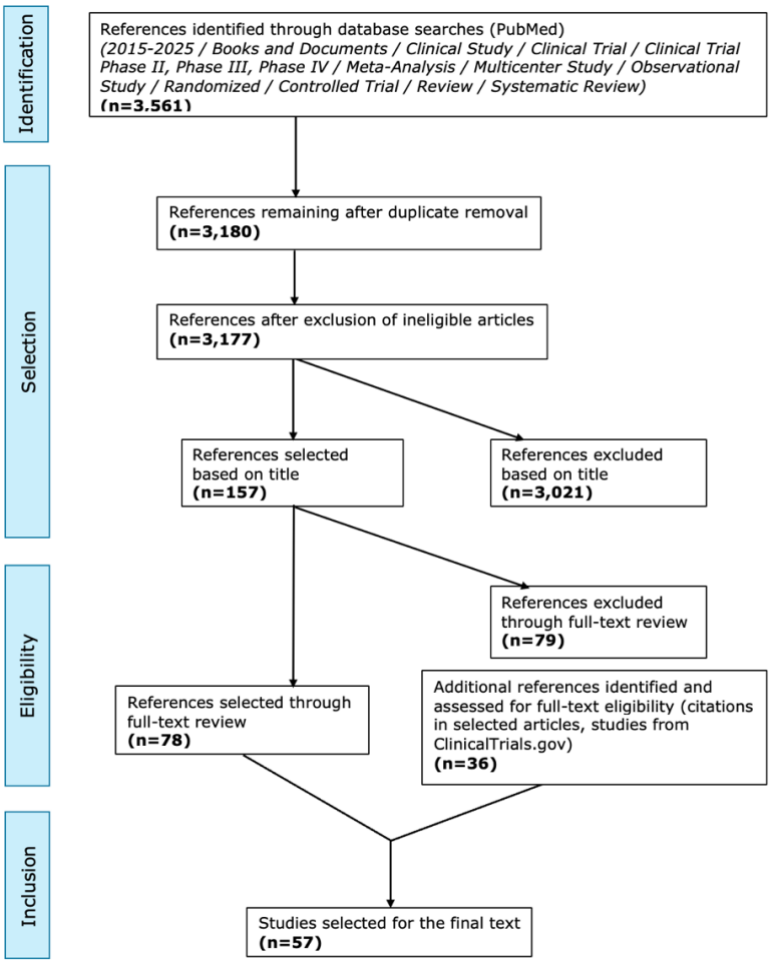

Figure 1: Search strategy flowchart

This flowchart summarizes the study selection process for the literature review.

3.2. Screening and prevention strategies in Type 1 Diabetes

3.2.1. Current screening methods: Overview of available biomarkers and genetic testing

β-cell autoantibodies are predictors of T1D and are currently the most reliable markers of preclinical stage of the disease. The presence of two or more autoantibodies against the four major autoantigens (insulin, glutamic acid decarboxylase, islet antigen 2, and zinc transporter 8) have been shown to confer the highest risk of T1D. This condition was recently defined as stage 1 T1D. (26) Autoantibodies in T1D are not believed to be pathogenic. (1)

a) Autoantibodies testing

Insulin Autoantibodies (IAA):

IAA are more commonly detected in children, particularly the youngest, and are therefore strongly associated with the highest risk of progression. (27) This early seroconversion is often associated with the DR4/DQ8 genetic predisposition haplotype. (28) However, IAA do not confer an independent risk in older children and adults. In fact, the development of IAA as the first autoantibodies before the age of 4 confers a cumulative risk of 73% of developing multiple autoantibodies in the following 5 years, whereas this risk is only 11% after the age of 4. (29) This underlines the importance of the age factor. The discovery of isolated IAA positivity in young children may justify closer monitoring. It should be noted that the IAA assay is not informative in people previously treated with insulin (e.g. for diabetes classified as gestational). (12)

Glutamic Acid Decarboxylase (GAD):

Anti-GAD are markers of early autoimmune activity in T1D. They appear between ages 3 and 5 years in children with either increased genetic risk or family history of T1D. (26) This later seroconversion is often associated with the DR3/DQ2 genetic predisposition haplotype (28) and is associated with slower progression. (12,26,27)

Islet Antigen 2 (IA-2):

The IA-2 autoantibodies are associated with rapid disease progression in both children and adults, and multiple autoantibody positivity. These are rarely the first autoantibodies to appear; they more often follow seroconversion of other autoantibodies, with a consequent later peak in incidence. (12) The appearance of IA-

2A, as a second-appearing autoantibody, is associated with a significantly higher risk of progression to T1D as compared with IAA or GADA. (26)

Zinc Transporter 8 (ZnT8):

Anti-ZnT8 autoantibodies are highly specific to T1D and emerge as a late-stage marker. Like anti-IA-2 antibodies, anti-ZnT8 antibodies tend to appear following other autoantibodies and are predictive of faster disease progression, especially in individuals over 10 years old (particularly those over 20) and/or with low genetic risk, especially in the absence of anti-IA-2. (12)

b) Genetic testing

In France, first-line Human Leucocyte Antigen (HLA) screening of at-risk individuals is not suitable for routine care, given its higher cost and the high frequency of predisposing alleles in the general population without increased risk of T1D. HLA genotyping can be used as a second-line procedure, in the presence of positive autoantibodies, for additional prognostic stratification. (12)

There are two HLA alleles at risk of predisposition to T1D: DQ2 and DQ8. (28) The presence of a single allele predisposing to T1D (DQ2, in particular DQB1*02:01 or DQ8, in particular DQB1*03:02) marks a moderate genetic risk, whereas the presence of two alleles (DQ2 and DQ8) marks a high genetic risk. The DQ6 allele (DQB1*06:02) is a protective allele and marks an overall low risk of T1D, even in the presence of positive autoantibodies. (12)

3.2.2. Recent advances in early detection: improved screening protocols and their impact on disease progression

a) Improved screening protocols

Both TrialNet (a U.S.-based consortium) and INNODIA (a European private/public partnership) began by screening relatives to maximize efficiency for enrollment in clinical studies. Five neonatal cohorts (TEDDY, DIPP/DIPP Novum, GPPAD, CASCADE, and PLEDGE) identify individuals at risk by screening for HLA class II alleles associated with T1D predisposition, before a second step of targeted screening for autoantibodies. Additionally, five programs, Fr1da, ASK, ELSA, EDENT1FI, and T1Detect, offer screening for children and/or adolescents in the general population, using simplified and less

costly autoantibody assays. A sixth study, T1DRA, is focused the adult general population. (12)

b) Impact on disease progression

These screening programs can prevent the onset of clinical symptoms. Early detection enables timely identification of individuals at risk, allowing for closer monitoring and participation in clinical trials or preventive programs. (12) While screening itself does not test therapies, individuals identified through such programs may be eligible for interventional studies aimed at delaying disease onset, such as trials on immune modulation therapies, which have shown promising results in clinical trials. (24)

One of the most immediate benefits of early screening, monitoring and regular follow-up of high-risk individuals is the reduction in the rate of DKA at diagnosis of stage 3 T1D. DKA rates fall from 25–62% to 4–6% with monitoring, with potential longer-term impacts to reduce HbA1c levels (23,30) and risk of complications. (23,31) Maintaining a low HbA1c level (<7%) significantly reduces the occurrence of microvascular and macrovascular complications in T1D. (3)

Some studies have reported a potential negative psychological impact on individuals who test positive for autoantibodies; however, this stress tends to diminish over time. Moreover, screening enables access to medical expertise to discuss results and provide ongoing education and monitoring, (23) including blood glucose monitoring, insulin administration, and recognizing symptoms of hyperglycemia or hypoglycemia. It is important to note that around 95% of relatives of individuals with T1D test negative for autoantibodies during screening, which can provide reassurance, particularly for families with a member already affected by the condition. (23)

3.2.3. France's first expert consensus on preclinical T1D screening and management

A first position statement by French experts on the screening and management of preclinical T1D was published in 2024, aiming to propose a national screening and management pathway for relatives of individuals living with T1D. They emphasize that the ability to screen for T1D at preclinical stages through autoantibody testing now enables early intervention, particularly in relatives of individuals living with T1D, who have a higher genetic risk than the general population. (12)

3.3. Emerging therapeutic targets for T1D

3.3.1. Disease modulation

The immunology of T1D is characterized by a complex interaction of immune cells and inflammatory processes that lead to the destruction of pancreatic β-cells by cytotoxic T cells. Dendritic cells, macrophages, and natural killer cells initiate the immune response. In the pancreatic lymph nodes, dendritic cells present antigens and secrete inflammatory mediators such as interleukin-12 (IL-12) and IL-15, activating autoreactive T cells, particularly $CD8^+$ T cells, which drive autoimmune attack on β-cells. T cell activation also necessitates costimulatory signals, such as those provided by the CD28 receptor. B cells also have an important role in T1D, most probably as antigen-presenting cells. Loss of B cell antigen presentation, but not loss of antibody secretion, can be sufficient to prevent the disease in the non-obese diabetic (NOD) mice model. The presence of pro-inflammatory cytokines, including Tumor Necrosis Factor (TNF) and IL-1β, has been implicated in the disease process, by exacerbating the immune response and contributing to β-cell destruction. These dysregulated immune responses result in the destruction of insulin producing β cells, leading to a profound insulopenia and the onset of symptomatic diabetes. (1)

3.3.2. Overview of therapeutic strategies

This section provides an overview of the therapeutic strategies under investigation for T1D. The following diagrams illustrate the mechanisms of action of the therapies being studied. A more detailed review of these therapeutic approaches will be provided in the subsequent sections.

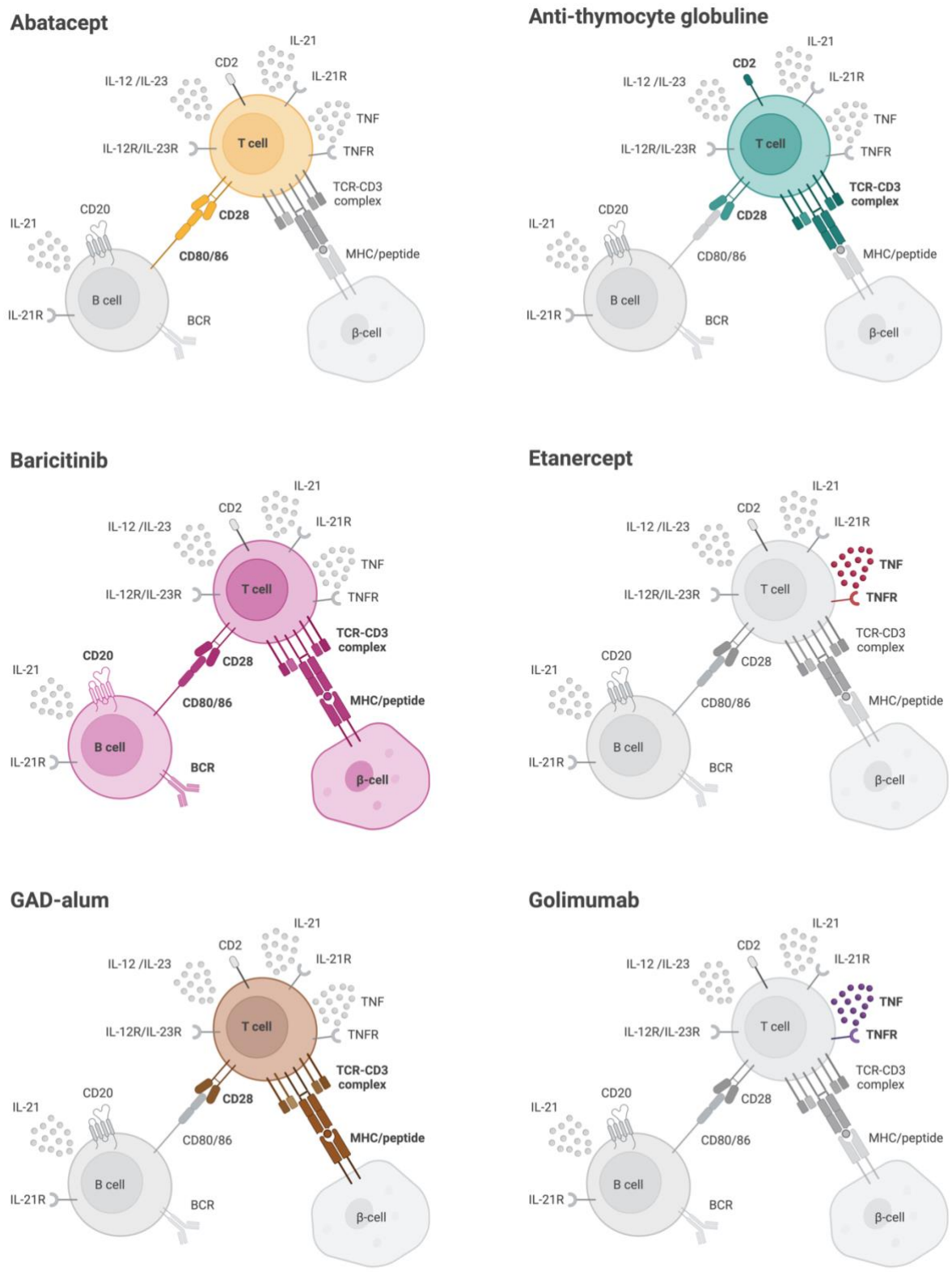

Figure 2: Drugs and mechanisms that have shown efficacy in T1D

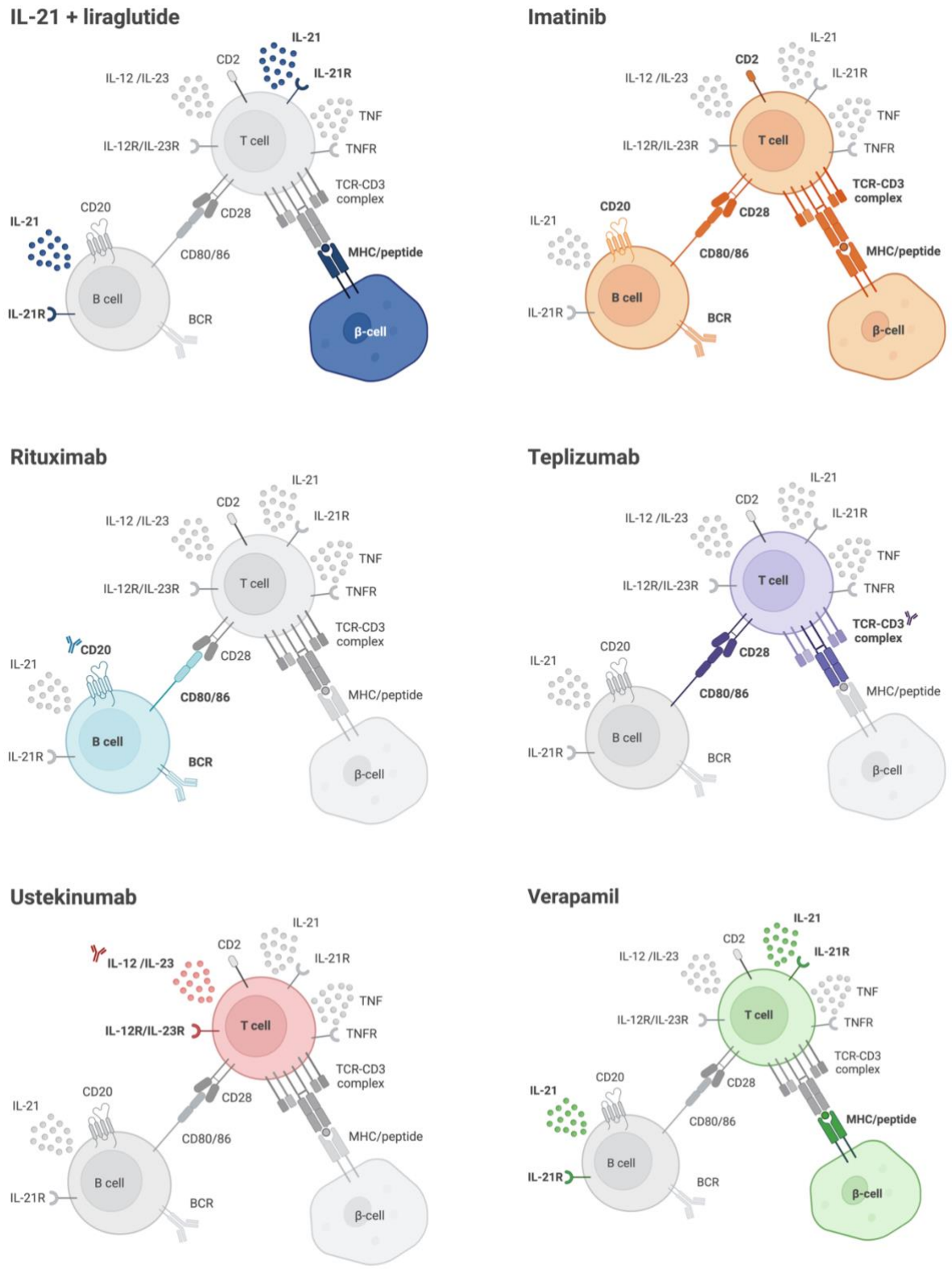

Figure 3: Drugs and mechanisms that have shown efficacy in T1D

These therapies target innate and inflammatory pathways, B cells, T cells, β-cells and costimulatory molecules. The main drug targets are highlighted using bold text and various colors. The illustrated T cells are general representations and may encompass multiple subsets, such as CD4⁺, CD8⁺, and TFH cells, among others. (1)

3.3.3. Several immunotherapies are being investigated in presymptomatic T1D

a) Abatacept

Abatacept is a cytotoxic T-lymphocyte antigen 4 associated Immunoglobulin (CTLA4Ig) that blocks the co-stimulatory signals required for T cell activation. It achieves this by binding to CD80/CD86 receptors on antigen-presenting cells, preventing their interaction with the CD28 molecule on T cells. This inhibition not only suppresses T cell activation, but also attenuates the downstream inflammatory cascade, modulating the immune response. This CTLA4Ig has been shown to be effective in treating several other autoimmune conditions, including juvenile idiopathic arthritis, psoriatic arthritis, and rheumatoid arthritis. (32)

Individuals with stage 1 T1D from the TrialNet pathway to prevention study were randomized to receive monthly abatacept (101 patients) or monthly placebo (111 patients) over 12 months. (32) The primary endpoint of the study was confirmed abnormal glucose tolerance (AGT) (stage 2) or clinical diabetes (stage 3), whether treatment of subjects at risk for diabetes with abatacept results in delay or prevention of AGT.

Abatacept treatment in individuals with stage 1 T1D impacted immune cell subsets and improved β-cell function, including a statistically significant improvement in C-peptide area under the curve (AUC) at month 12. However, it did not meet the predefined criteria for delaying progression to stage 2 or stage 3 diabetes. While abatacept improved insulin secretion, it did not significantly delay progression to later stages of T1D. One limitation of this study is the sample size, which may have been too small to detect a statistical difference in progression to stage 2 T1D.

Abatacept infusions were generally well-tolerated, with no significant differences in adverse events between the groups, except for more skin/connective tissue disorders in the abatacept group. Five serious adverse events occurred (2 in the abatacept group, 3 in the placebo). Two participants in the abatacept group were diagnosed with breast and thyroid cancers, raising long-term risk concerns.

b) Teplizumab

The most advanced immunotherapy in T1D is teplizumab, a humanized Fc receptor nonbinding anti-CD3 monoclonal antibody (mAb). (2) This mAb induces a state of operational tolerance in T1D patients. By binding to CD3 on T cells, it reduces CD3

expression, crucial for T cell activation, leading to altered T cell subsets. Initially, teplizumab partially activates $CD4^+$ and $CD8^+$ T cells (33), but over time, these cells exhibit exhaustion and regulatory phenotypes, shifting the immune response towards tolerance. (34,35) A long-term follow-up study of responders from the AbATE trial has shown an increased programmed cell death protein 1 (PD1) expression on $CD8^+$ T cells and an increase in $PD1^+$ central memory $CD8^+$ T cells and anergic $CD8^+$ T cells, which may explain the long-term effects of teplizumab. (36) Teplizumab reduces IL7R expression in $CD8^+$ T cells, which is needed for their growth and expansion, thereby preventing the expansion of autoantigen-reactive $CD8^+$ T cells. Long-term effects include sustained changes in T cell populations and signaling pathways, with persistent alterations in T cell receptor and activation pathways, which are essential for maintaining immune homeostasis and preventing autoimmune responses. These changes may support long-term T1D management and operational tolerance. (34)

The TN-10 study, a phase 2, randomized, placebo-controlled, double-blind trial, evaluated the efficacy of teplizumab in delaying the onset of T1D in relatives at high risk. (24)
In total, 93% of participants in the teplizumab group (41 of 44) and 88% of participants in the placebo group (28 of 32) completed the 14-day course of the assigned trial agent. The duration of follow-up was more than 3 years in 57 participants (75%).
A single course of teplizumab delayed T1D diagnosis in 19 of 44 participants (43%), with an annualized diagnosis rate of 14.9%, compared to 23 of 32 participants (72%) in the placebo group, which had a rate of 35.9% per year. The median time to diagnosis was 48.4 months in the teplizumab group *versus* 24.4 months in the placebo group. The hazard ratio remained significant after adjusting for age, oral glucose tolerance test results, and anti-GAD65 antibody presence.
In the first year after trial entry, there were 17 out of 42 participants (40%) in the overall trial population that progressed to a clinical T1D. This was greater than in year 2 (10 participants, 24%), year 3 (6 participants, 14%), or year 4 (5 participants, 12%). The largest effect of teplizumab treatment was found in the first year: diabetes was diagnosed in only 3 of 44 participants (7%) in the teplizumab group, in contrast to 14 of 32 participants (44%) in the placebo group.
The results of the TN-10 study highlighted that teplizumab effectively delayed T1D onset in high-risk individuals, highlighting its potential as a preventive treatment.

In a follow-up study (34) of 74 participants from the TN10 trial, another group of experts monitored them for a median of 80.46 months. The median time to stage 3 T1D was

52.2 months with teplizumab compared to 27.3 months with placebo. At follow-up, 36% (16/44) of teplizumab-treated patients had not developed stage 3 T1D, compared to 12.5% (4/32) in the placebo group, confirming its efficacy in delaying progression for over five years in some cases.

The safety analysis of teplizumab confirmed its immunomodulatory nature rather than immunosuppressive effects, (37) as it preserves immune defense. There was no significant increase in serious infections compared to the placebo group. Expected adverse events included rash and transient lymphopenia, observed in both children and adults, aligning with the known profile of immunomodulatory treatments. (24)
The response to teplizumab varied based on HLA profile and the presence of autoantibodies. A stronger response was observed in patients with HLA-DR4 and without HLA-DR3, (24) suggesting that HLA profile influences the drug's efficacy in delaying clinical T1D onset. Additionally, the treatment was significantly more effective, compared to placebo, in participants without anti–ZnT8 antibodies, while the presence or absence of other autoantibodies showed no association with clinical response. (24)

Teplizumab was recently approved by the Food and Drug Administration (FDA) for the treatment of stage 2 T1D, but not for the treatment of stage 3 T1D (new-onset, clinically evident). (12,38)

3.3.4. Several therapies are being studied in recent onset stage 3 T1D

a) Abatacept

In this multicenter, double-blind, randomized controlled trial, 112 patients aged 6-45 years recently diagnosed with T1D were randomly assigned (2:1) to receive abatacept or placebo infusions intravenously on days 1, 14, 28, and monthly over 2 years. (39)
Primary outcome was baseline-adjusted geometric mean 2-hour AUC serum C-peptide following a mixed meal tolerance test (MMTT) at two years.
Adjusted C-peptide AUC was significantly higher at two years with abatacept *versus* placebo. The difference between groups was present throughout the trial, with an estimated 9.6 months' delay in decline with abatacept. There was lower HbA1c but similar insulin use.
Co-stimulation modulation with abatacept slowed decline of β-cell function over two years. The beneficial effect suggests that T cell activation still occurs around the time of clinical diagnosis of T1D. Yet, despite continued administration of abatacept over 24

months, the decline in β-cell function with abatacept was parallel to that with placebo after six months of treatment, suggesting that T cell activation may increase over time. Abatacept demonstrated a favorable safety profile, with infusion-related adverse events occurring in only 1.9% (27/2514) of infusions. There was no significant increase in infections, including Epstein-Barr Virus, or in neutropenia. The overall adverse event rate was low, with no significant difference between the abatacept and placebo groups. Two cases of severe hypoglycemia were reported during the study, one in each group. A key limitation for the young trial population is that live vaccines cannot be administered within three months of starting abatacept.

b) Anti IL21 + liraglutide

The combination of an anti-IL-21 antibody (for transient and low-grade immunomodulation, as IL-21 promotes $CD8^+$ T-cell trafficking from lymph nodes and the exocrine pancreas to pancreatic islets) and liraglutide (a Glucagon-Like Peptide-1 (GLP-1) receptor agonist that improves β-cell function by reducing stress, preventing apoptosis, protecting insulin secretion, and correcting proinsulin-to-insulin processing defects) offers a potential strategy to enhance β-cell survival with fewer complications compared to traditional immunomodulation. (40)

308 participants, aged 18–45 years with recently diagnosed T1D and residual β-cell function, were randomly allocated to combination of anti-IL-21 and liraglutide, to liraglutide only, to anti-IL-21 only and to placebo (1:1:1:1). (40) The primary outcome was the change in MMTT-stimulated C-peptide concentration from baseline to week 54, measured via the AUC over a 4-hour period.
Compared with placebo, the primary outcome was significantly smaller with combination treatment, but not with anti-IL-21 alone or liraglutide alone. The combination of anti-IL-21 and liraglutide could preserve β-cell function in recently diagnosed T1D. The efficacy of this combination appeared to be like that seen in trials of other disease-modifying interventions in T1D, but with a seemingly better safety profile.
The reported adverse events were few and mild. The most frequently reported adverse events were gastrointestinal disorders, which are common side effects associated with GLP-1 receptor agonists, suggesting a favorable safety profile. The long-term safety and efficacy of this combination therapy remain to be assessed in a phase 3 trial.

c) Low-dose anti-thymocyte globulin (ATG)

A previous randomized, placebo-controlled, single-masked pilot clinical trial demonstrated that combination therapy with low-dose anti-thymocyte globulin/granulocyte colony-stimulating factor (ATG/GCSF) preserved C-peptide in clinical stage 3 T1D. (41)

To explore the potential of low-dose ATG/GCSF or low-dose ATG monotherapy to preserve β-cell function in new-onset T1D, the Type 1 Diabetes TrialNet Study Group conducted a three-arm, randomized, double-masked, placebo-controlled trial (low-dose ATG/GCSF, low-dose ATG, and placebo) in persons with new-onset T1D (89 patients aged 12–45 years diagnosed with T1D for <100 days). (42)
The primary end point was mean AUC C-peptide during a 2-hour MMTT 1 year after initiation of therapy. The 1-year mean AUC C-peptide was significantly higher in subjects treated with ATG *versus* placebo but not in those treated with ATG/GCSF *versus* placebo. In addition, HbA1c was significantly reduced at 1 year in subjects treated with ATG and ATG/GCSF. Low-dose ATG slowed decline of C-peptide and reduced HbA1c in new-onset T1D.
In this study, low-dose ATG had a favorable safety profile with manageable adverse effects. Notable events included serum sickness and cytokine release, which were predictable and manageable. No serious infections or grade 4 adverse events were reported, indicating a relatively safe profile.

The follow-up was extended to two years with the same patients from the original study. (43) At two years, the average stimulated C-peptide response was significantly higher in participants treated with ATG compared to placebo but not in those treated with ATG/GCSF. HbA1c levels were significantly lower at two years in both the ATG and ATG/GCSF groups compared to placebo.
There were no increases in adverse effects between the 1- and 2-year endpoints for subjects treated with ATG or ATG/GCSF. In fact, the placebo group experienced nearly twice as many adverse effects compared to the actively treated groups during the same period, indicating a potentially favorable safety profile for ATG.

d) Baricitinib

Baricitinib, a Janus kinase (JAK) inhibitor, blocks cytokine signaling and is an effective disease-modifying treatment for several autoimmune diseases. Autoreactive $CD8^+$ T

cells in T1D target β-cells via HLA class I molecules, with JAK-STAT signaling playing a critical role in $CD8^+$ T cell activation and immune synapse formation, while JAK inhibitors disrupt these processes and prevent β-cell death. (22)

In a phase 2, double-blind, randomized, placebo-controlled trial clinical a total of 91 patients received baricitinib (60 patients) or placebo (31 patients). (22) The primary outcome was the mean C-peptide level, determined from the AUC–time curve, during a 2-hour MMTT at week 48.
As a result, the median of the mixed-meal–stimulated mean C-peptide level at week 48 was significantly higher in the baricitinib group than in the placebo group. In patients with T1D of recent onset (children and adults), daily treatment with baricitinib over 48 weeks appeared to preserve β-cell function as estimated by this primary outcome. The acceptable safety profile of 1 year of baricitinib therapy in this trial appeared to justify further evaluation of longer treatment durations in populations with T1D.
In fact, this treatment has been used for many years as a treatment for juvenile idiopathic arthritis, and the safety profile of JAK inhibitors has been acceptable.

e) Etanercept

Etanercept, an anti-TNFα fusion protein that binds to and removes TNFα from circulation, thereby blocking the biological activity of this inflammatory cytokine. (44)
TNF-α is a pro-inflammatory cytokine implicated in the pathogenesis of several autoimmune conditions. Produced by activated macrophages, dendritic cells, $CD4^+$ lymphocytes, and other cells, TNF-α initiates a cascade of responses including the production of IL-1β and IL-6, enhanced expression of adhesion molecules, and activation of apoptotic and cytotoxic response. TNF-α has been identified as a critical regulator in the progression of T1D. (45)

In a 24-week double-blind, randomized, placebo-controlled study, 18 subjects (aged 7.8–18.2 years) were randomly assigned to receive either placebo or etanercept. (44)
The primary end points of this study were percent change from baseline for HbA1c and for C-peptide AUC.
HbA1c levels were higher in the etanercept group compared to the placebo group at baseline and after 4 weeks, though not significantly. From week 8, HbA1c values were lower in the etanercept group, with a significant difference at week 24. The percent decrease in HbA1c from baseline was consistently greater in the etanercept group from week 8 to week 24. At the 4- and 12-week washout visits, HbA1c remained lower in the

etanercept group, with significance at the 4-week washout. The percent decrease in HbA1c continued to be significantly higher in the etanercept group at both washout points. C-peptide AUC increased in the etanercept group and decreased in the placebo group by week 24.

Etanercept has shown a favorable safety profile in pediatric patients with new-onset T1D, with no severe adverse events reported during the study. Mild adverse effects included self-resolving paresthesia and increased cold symptoms in the etanercept group, along with some abdominal pain in one patient, but these did not significantly impact daily activities or school attendance.

f) GAD-alum + oral vitamin D (Dyamid®)

DIAGNODE-2 was a phase 2b, multicenter, randomized, placebo-controlled, double-blind trial of 109 recent-onset T1D patients aged 12 to 24 years with GAD65 antibodies and fasting C-peptide > 120 pmol/L, which randomized patients to 3 intralymphatic injections of autoantigen therapy with recombinant human GAD65 in alum (GAD-alum) and oral vitamin D, or placebo. (46) The results for exploratory endpoints were assessed by 14-day CGM at months 0, 6, and 15.

A total of 98 patients with CGM recordings of sufficient quality were included in the study (DR3-DQ2-positive group: 27 GAD-alum-treated and 15 placebo-treated). Among DR3-DQ2-positive patients, the percent of time in range (TIR, 3.9-10 mmol/L) declined less from baseline to month 15 in the GAD-alum-treated group compared to the placebo group (-5.1% vs -16.7%, respectively), with significant improvements observed in the glucose management indicator. No safety data was available, but hypoglycemia rates remained unchanged. Compared to placebo, GAD-alum attenuated the increase in glycemic variability observed in both groups.

Intralymphatic GAD-alum improves glycemic control in recently diagnosed T1D patients carrying HLA DR3-DQ2.

g) Golimumab

Golimumab is a human mAb specific for TNF*a* that has already been approved for the treatment of several autoimmune conditions in adults and children. (47)

In this phase 2, multicenter, placebo-controlled, double-blind, parallel-group trial, (47) children and young adults (age range, 6 to 21 years) with newly diagnosed T1D were

randomly assigned, in a 2:1 ratio, to receive subcutaneous golimumab or placebo for 52 weeks. The primary end point was endogenous insulin production, as assessed according to the C-peptide AUC in response to a 4-hour MMTT at week 52.
At week 52, the 4-hour C-peptide AUC was significantly higher in the golimumab group compared to the placebo group. Additionally, 41% of participants in the golimumab group experienced either an increase in C-peptide AUC or a decrease of no more than 5% through week 52. Golimumab resulted in better endogenous insulin production than placebo, as indicated by the 4-hour C-peptide AUC.
91% of golimumab participants experienced adverse events, compared to 82% in the placebo group. Hypoglycemia occurred in 23% of the golimumab group, with mild to moderate infections in 71%. Neutropenia was noted in some golimumab recipients, but no serious infections or other major complications were reported.

h) Imatinib

Imatinib, a tyrosine kinase inhibitor originally approved for chronic myelogenous leukemia, (48) has shown potential in T1D by targeting both immunologic and metabolic pathways. (49) Preclinical studies demonstrated its ability to prevent T1D and induce remission of new-onset diabetes in NOD, possibly by reducing endoplasmic reticulum stress in β-cells, decreasing apoptosis, and improving insulin sensitivity. (49,50)

In this phase 2, randomized, placebo-controlled, double-blinded clinical trial, (49) 67 patients with recent-onset T1D, aged 18-45 years, and with peak C-peptide ≥ 200 pmol/L on MMTT were randomly assigned 2:1 to receive either imatinib or matching placebo for 26 weeks, respectively. The primary endpoint was the 2-hour AUC C-peptide response to MMTT in the imatinib group *versus* placebo group at 12 months, with further observation out to 24 months.
The study achieved its primary endpoint, with a significant adjusted mean difference in 2-hour C-peptide AUC between the imatinib and placebo groups in response to an MMTT at 12 months. However, this effect was not maintained at 24 months.
In this study, 71% of imatinib recipients experienced grade 2 or worse adverse events, *versus* 59% in the placebo group. Due to side effects, 38% of the imatinib group required dose adjustments, and 13% discontinued treatment. Most adverse events were mild to moderate, indicating a manageable safety profile.

i) Rituximab

Rituximab, an anti-CD20 mAb, can deplete B cells involved in the autoimmune attack on islets as antigen-presenting cell. (51)

In a double-blind study, 87 patients between 8 and 40 years of age who had newly diagnosed T1D were assigned to receive infusions of rituximab or placebo on days 1, 8, 15, and 22 of the study. (51) The primary outcome, assessed 1 year after the first infusion, was the geometric mean AUC for the serum C-peptide level during the first 2 hours of a MMTT. Then, subjects were further followed with additional MMTTs every 6 months. (52)

At 1 year, the mean AUC for the level of C peptide was significantly higher in the rituximab group than in the placebo group. Between 3 months and 12 months, the rate of decline in C-peptide levels in the rituximab group was significantly less than that in the placebo group. (51) Over 30 months, AUC, insulin dose, and HbA1c were similar for rituximab and placebo. However, in evaluating change in C-peptide over the entire follow-up period, the rituximab group means were significantly larger as compared within assessment times with the placebo group means using a global test. B cells recovered to baseline values by 18 months. (52)

Like several other immunotherapeutic approaches tested, in recent-onset T1D, rituximab delayed the fall in C-peptide but does not appear to fundamentally alter the underlying pathophysiology of the disease. (52)

93% of rituximab-treated patients experienced infusion reactions *versus* 23% in the placebo group, with 392 adverse events reported compared to 148 in the placebo group. Most events were grade 1 or 2, with only six grade 3 events and no grade 4 events. (51) Long-term follow-up showed a decline in adverse events after the first year, reinforcing a largely positive safety profile. (52)

j) Teplizumab

The PROTECT study evaluated teplizumab's impact on β-cell function in individuals newly diagnosed with T1D. (37) In this phase 3, randomized, placebo-controlled trial, children and adolescents assigned to receive teplizumab or placebo for two 12-day courses. The primary end point was the change from baseline in β-cell function, measured by stimulated C-peptide levels during a 4-hour MMTT at week 78. At total, patients treated with teplizumab (217 patients) had significantly higher stimulated C-peptide levels than patients receiving placebo (111 patients) at week 78. Among patients treated with teplizumab, 94.9% maintained a clinically meaningful peak C-

peptide level ≥ 200 pmol/L, compared to 79.2% in the placebo group. Finally, the results of this study showed that teplizumab effectively preserved β-cell function in newly diagnosed T1D patients, highlighting its role in extending residual insulin production.

Teplizumab was associated with a variety of mild to moderate adverse effects in this study. The most common side effects included headache, gastrointestinal symptoms, rash, lymphopenia, and mild cytokine release syndrome, which were generally transient and resolved spontaneously. Severe hypoglycemia occurred in 13.4% of patients treated with teplizumab, compared to 16.2% in the placebo group. No cases of DKA were reported, indicating a favorable safety profile for teplizumab.

k) Ustekinumab

Ustekinumab is a mAb targeting the shared p40 subunit of IL-12 and IL-23, neutralizing IL-12 and IL-23, and thus modulating T helper 1 (TH1) and TH17 responses, which play a role in the pathogenesis of T1D. TH1 and TH17 T cells respectively secrete IFN-γ and IL-17 that promote inflammation and immune cell activation. (53)

In this multicenter, double-blind, randomized phase 2 trial evaluating ustekinumab in adolescents with T1D, 72 adolescents aged 12-18 years received either ustekinumab or placebo. (54) The primary outcome was the change in C-peptide AUC during a 2-hour MMTT at 52 weeks.

At 12 months, the ustekinumab group had a 49% higher C-peptide AUC compared to the placebo group. The trial results indicated that ustekinumab may effectively preserved C-peptide levels in adolescents with T1D, particularly after a delayed onset of action. However, secondary outcomes related to glycemic control did not show significant differences between the treatment and placebo groups. Ustekinumab was well tolerated with no serious treatment-related adverse events, and the safety profile was consistent with previous studies.

l) Verapamil

Thioredoxin-interacting protein (TXNIP) overexpression has been shown to induce pancreatic β-cell apoptosis and be involved in glucotoxicity-induced β-cell death in mouse models. (55) Verapamil, an antihypertensive calcium channel blocker, reduces TXNIP expression and β-cell apoptosis (56) and may be beneficial in β-cell preservation after a T1D diagnosis. (38)

In a randomized double-blind placebo-controlled phase 2 clinical trial, 24 patients receive either verapamil or placebo for 1 year. (57) Verapamil treatment, compared with placebo was well tolerated and associated with an improved mixed-meal-stimulated C-peptide AUC, a measure of endogenous β-cell function, at 3 and 12 months (prespecified primary endpoint).

Verapamil demonstrated a favorable safety profile, with mild adverse effects primarily limited to constipation, a common side effect of the drug, which did not necessitate medical intervention. No severe adverse events, such as hypotension or significant electrocardiogram changes, were reported. Throughout the trial, participants maintained normal blood pressure and heart rate, with no severe hypoglycemic episodes requiring assistance.

Thus, addition of once-daily oral verapamil may be a safe and effective novel approach to promote endogenous β-cell function and reduce insulin requirements and hypoglycemic episodes in adult individuals with recent-onset T1D.

Another clinical study has been conducted, this time focusing on a pediatric population. This double-blind, randomized clinical trial (38) includes children and adolescents aged 7 to 17 years with newly diagnosed T1D.

The primary outcome was area AUC values for C-peptide level (a measure of pancreatic β-cell function) stimulated by a MMTT at 52 weeks from diagnosis of T1D.

In the verapamil group, the mean C-peptide AUC remained relatively stable from baseline to 52 weeks after diagnosis, whereas in the placebo group, it declined over the same period. The adjusted treatment difference at 52 weeks indicated higher C-peptide levels with verapamil compared to placebo. After an initial increase in both groups by 13 weeks, the mean C-peptide AUC decreased in the placebo group, while it remained stable in the verapamil group until 26 weeks before declining. In children and adolescents with newly diagnosed T1D, verapamil partially preserved stimulated C-peptide secretion at 52 weeks from diagnosis compared with placebo.

Verapamil showed a favorable safety profile in this study in T1D, with similar adverse event rates to placebo. Treatment-related events were mostly mild, including electrocardiogram abnormalities and hypotension, with no significant impact on blood pressure or heart rate.

3.4. Evidence supporting C-peptide and HbA1c as predicting factors of T1D complications

As demonstrated in the earlier sections of this article, previous data have shown that different new therapies impact C-peptide concentration and HbA1c levels. The influence of these factors on the acute and chronic complications of T1D will now be explored.

Higher C-peptide levels, maintained through certain immunotherapies, were associated with a reduced risk of DKA. Individuals with C-peptide levels >200 pmol/L had lower rates of DKA-related hospitalizations and mortality compared to those with levels <5 pmol/L. (21)

Furthermore, higher C-peptide levels were associated with a reduction in long-term complications of T1D. Regarding retinopathy, individuals with C-peptide ≥30 pmol/L had lower rates of both prevalent and incident retinopathy compared to those with levels <5 pmol/L, with a linear relationship between baseline C-peptide and incident retinopathy. (21) In nephropathy, while higher C-peptide levels correlated with a lower prevalence of Chronic Kidney Disease (CKD) stage 3 at baseline, incident CKD stage 3 was not directly related to C-peptide when adjusting for baseline estimated glomerular filtration rate. (21) Additionally, C-peptide levels between 30–200 pmol/L were associated with a lower incidence of self-reported hypoglycemia unawareness. (21)
C-peptide levels ≥200 pmol/L were associated with lower HbA1c levels, which may offer therapeutic benefits for patients with T1D. (21) Data from the DCCT demonstrated that maintaining an HbA1c level <7%, particularly in the early stages following T1D diagnosis (due to the phenomenon of "metabolic memory"), significantly reduced the risk of both microvascular and macrovascular complications associated with T1D. (3)
In a linear regression model adjusted for sex, Body Mass Index (BMI), age at diagnosis, and diabetes duration, individuals with C-peptide levels ≥200 pmol/L required lower daily insulin doses compared to those with C-peptide <5 pmol/L. (21) This suggests that preserved endogenous insulin secretion, supported by certain immunotherapies, may reduce exogenous insulin needs in individuals with T1D.

Increasing numbers of studies examined the relationship between detectable C-peptide levels and improved glycemic control, particularly in terms of reduced glucose variability in individuals with T1D. Studies have shown that individuals with detectable C-peptide levels demonstrated better glycemic control, as indicated by lower HbA1c levels and reduced daily insulin requirements. (58) Furthermore, clinically significant

improvements in glycemic control, as measured by CGM, were observed in individuals with high (>400 pmol/L) mixed meal–stimulated C-peptide levels. (58)

4. Discussion

The management of T1D has seen significant progress in recent years, particularly with advancements in prevention, screening, early detection, and emerging therapeutic targets. Prevention strategies are evolving, with immunotherapies showing promising results in delaying disease onset. Numerous immunotherapies are currently being investigated, with most trials in phase 2, indicating promising prospects for disease-modifying treatments. However, phase 3 trials are essential to assess long-term safety and efficacy in both pediatric and adult populations before these therapies can be widely implemented.

The FDA has approved Tzield® (teplizumab) injection to delay the onset of stage 3 T1D in adults and pediatric patients 8 years and older who have stage 2 T1D. (12) This opens the door to early intervention and targeted therapies aimed at immune modulation to prevent the destruction of insulin-producing beta cells. It is the only therapy that has been approved by the FDA for delaying the onset of stage 3 T1D in individuals at stage 2, but it has not yet been authorized for recently diagnosed stage 3 patients. (38)

The care of T1D presents key challenges. Although C-peptide is now accepted by regulatory authorities as a primary endpoint in trials of interventions to preserve or restore β-cell function, there is not yet a consensus on what level of C-peptide secretion constitutes a clinically useful therapeutic effect. (21) Currently, the primary efficacy measure in pivotal studies is the time to progression to stage 3 diabetes (with people with stage 2 DT1), highlighting the need for a standardized definition of clinically meaningful C-peptide preservation.

Another key challenge is the absence of a national screening program in many countries, including France. While, on September 2023, the Italian Parliament approved a law introducing a nationwide screening T1D and coeliac disease in the general population aged 1–17 years as part of the public health program aimed at reducing the effects of these chronic diseases. (59) This gap highlights the importance of the recent French experts position statement, which advocates for the necessity of early screening for relatives of individuals living with T1D to improve outcomes for subjects at risk. (12)

Early screening has been shown to have beneficial effects on the quality of life of T1D patients and their families. A positive screening result without glycemic disturbances could cause anxiety for the individual and/or their family, though this stress typically normalized within 12 months. A cohort of children at high genetic risk for T1D showed better psychological adaptation within the family, with parents reporting improved quality of life for their child and less stress during the first year after diagnosis compared to controls with clinically diagnosed T1D who had not been screened. (12)
Moreover, early screening could optimize the efficiency of patient recruitment for clinical trials, (12) ensuring that the right individuals are identified for potential therapeutic interventions

The first limitation of this work is the lack of external validation. However, the therapies identified in the reviewed articles have been presented at various conferences, including *International Society for Pediatric and Adolescent Diabete*s in Lisbon 2024, and *Immunology of Diabetes Congress* in Bruges 2024.
Then, this review focused on immunotherapies and verapamil in phase 2 and 3 clinical trials with published results. However, numerous other therapies are currently being investigated, though their official results have not yet been published. Notable examples include BMF-219, IMCY-0098, ladarixin, and tolimidone.

Furthermore, new therapies, such as pancreatic islet transplantation, are offering promising avenues for the management of T1D. (60) Cell-based therapies, including islet transplantation and stem cell therapies, focus on restoring insulin-producing β-cell. These approaches offer the potential to reduce or even eliminate the need for insulin injections, significantly improving the quality of life for individuals with T1D. However, challenges such as immune rejection, long-term efficacy, and accessibility remain key hurdles to overcome. (60)

Overall, while significant progress has been made, the path to a cure for T1D remains challenging. Continued multidisciplinary efforts are essential to unlock more effective treatments, reduce the burden of complications, and achieve the goal of preventing and possibly reversing T1D. This new approach requires adaptation from physicians. Early screening programs, revised patient care strategies, and updated clinical guidelines will be necessary to integrate these new therapies into routine practice, ensuring optimal patient outcomes.

Discussion

1. Retour sur l'intérêt et les enjeux de cette thèse

Ce travail a un intérêt scientifique et clinique, en effet la prise en charge du DT1 est fondée sur l'insulinothérapie depuis plus d'un siècle (l'insuline a été découverte en 1921 par les docteurs Frederick Banting et Charles Beset (2)). Mais cette prise en charge évolue, de nouvelles approches thérapeutiques sont en cours d'étude depuis plusieurs années et montrent des résultats intéressants.

Cette thèse rappelle aussi l'importance de savoir questionner un paradigme établi depuis près d'un siècle pour améliorer la qualité de vie des patients et optimiser les soins.

2. Les défis de l'introduction des immunothérapies dans la prise en charge du DT1

Ces nouvelles perspectives de prise en charge rencontrent de nombreux défis. Ce sont des innovations qui bousculent le modèle classique : le passage d'une prise en charge purement substitutive (insuline) à une approche modifiant la maladie, grâce aux immunothérapies, certaines connues depuis plus de 20 ans. En effet les résultats d'étude de l'intérêt de l'etanercept dans le DT1 ont été établis en 2011. (44)

De plus, l'introduction de ces nouvelles thérapies se heurte à des obstacles réglementaires et méthodologiques, nécessitant des ajustements dans les critères d'évaluation, les processus d'approbation et les protocoles cliniques afin de garantir leur efficacité et leur sécurité à long terme. Les autorités de santé, telles que la FDA aux Etats-Unis et la *European Medicines Agency* (EMA) en Europe ont la nécessité d'identifier un critère d'évaluation primaire pertinent pour l'évaluation de ces nouveaux traitements. La difficulté pour ces autorités de santé est de comparer ces thérapies avec une prise en charge standardisée et bien établie, et d'en mesure le ratio bénéfice/risque. En outre, le temps, très souvent long, des processus d'approbation et les exigences en matière de preuves d'efficacité et de sécurité à long terme sont des défis que rencontrent les différents laboratoires pharmaceutiques. La sécurité et l'efficacité clinique à long terme des thérapies présentées devront être testées. Ces études seront essentielles pour obtenir l'approbation des autorités de santé et faciliter leur intégration dans la pratique courante. Des programmes nationaux de détection précoce pourraient orienter les patients dont les résultats sont positifs pour des anticorps spécifiques vers

divers essais cliniques et ainsi leur permettre d'accéder à de nouveaux traitements en cours d'évaluation. (12)

3. Une question non abordée dans ce travail, l'impact économique du dépistage précoce et des immunothérapies

En France, l'intégration du dépistage du DT1 dans les politiques nationales de santé constitue un objectif prioritaire pour certains soignants. Cette approche vise à faciliter le diagnostic et la prise en charge précoces, afin de réduire l'impact de la maladie sur les individus et le système de santé. (12)

A court terme, ces thérapies pourraient présenter des bénéfices économiques, notamment grâce à une réduction des hospitalisations liées aux complications aigues résultant d'un diagnostic tardif du stade 3 du DT1, en particulier pour les populations pédiatriques où les coûts peuvent s'accumuler rapidement. (12)

De plus, le dépistage et l'intervention précoces pour le DT1 peuvent réduire considérablement les dépenses de santé à long terme. En identifiant les personnes à risque et en prenant en charge la maladie avant qu'elle n'atteigne le stade clinique, le besoin de traitements coûteux et d'hospitalisations peut être minimisé. Cela est d'autant plus important que les complications du DT1 (notamment les maladies cardiovasculaires et les problèmes rénaux), peuvent entraîner des coûts de santé importants au fil du temps. (12) De plus, des niveaux plus élevés de peptide C, préservés grâce à certaines immunothérapies, sont associés à une réduction des complications à long terme du DT1. (21)

Cependant, le coût pour les patients de ces nouvelles immunothérapies pourrait être un frein potentiel à leur déploiement à grande échelle en fonction des systèmes de santé des différents pays. Cela pourrait avoir un impact sur les systèmes de remboursement et l'accès aux traitements des patients.

Une perspective de recherche future serait d'étudier et de chiffrer l'impact médico-économique des immunothérapies à court et long termes au sein de différents pays. Il serait également intéressant de comparer cet impact médico-économique avec d'autres stratégies de prise en charge innovantes, telles que le pancréas artificiel et les thérapies cellulaires dans le cadre du DT1.

4. Conclusion

Cette thèse présente une nouvelle ère dans la prise en charge médicamenteuse du DT1. L'arrivée des immunothérapies dans le DT1 marque une évolution majeure dans le traitement de cette pathologie, avec une nouvelle prise en charge des patients : traiter avant que les symptômes n'arrivent ou rapidement après le diagnostic de la maladie, dépister les patients à risque grâce à la recherche d'auto-anticorps… Cependant, leur intégration dans la pratique clinique nécessite encore des adaptations réglementaires, économiques et organisationnelles. Les diabétologues, endocrinologues et pédiatres seront au cœur de cette nouvelle approche de la prise en charge du DT1. L'intégration des immunothérapies et des nouvelles stratégies thérapeutiques les amènera à adapter leurs recommandations, notamment en matière de suivi, d'éducation thérapeutique et de gestion des traitements innovants. Leur rôle sera essentiel pour accompagner les patients et leurs familles dans cette transition, optimiser l'adhésion aux nouvelles prises en charge et anticiper d'éventuels effets indésirables.

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Annexes

1. Annexe 1 : Several strategies are being investigated in presymptomatic T1D

Agent	Description	Mechanism of action	Trial Phase	Primary Endpoint
Abatacept	CTLA4Ig	Blocks CD28 costimulatory signals	Phase 2	Time from randomization (Stage 1 T1D) to consecutively confirmed abnormal glucose tolerance test result or to Stage 3 T1D (32)
Teplizumab	Anti-CD3 mAb	Targets CD3 on $CD8^+$ and $CD4^+$ T cells	Phase 2	Time to diagnosis of Stage 3 T1D in people with Stage 2 T1D (24)

Tableau 1 : Several therapies are being studied in presymptomatic T1D

This table summarizes various strategies under investigation for presymptomatic autoimmune T1D. It outlines the molecules being studied, their description, mechanism of action, and primary endpoint.

2. Annexe 2 : Several therapies are being studied in recent onset stage 3 T1D

Agent	Description	Mechanism of action	Trial Phase	Primary Endpoint
Abatacept	CTLA4Ig	Blocks CD28 costimulatory signals	Phase2	AUC of stimulated C-peptide response over the first 2 hours of a 4-hour MMTT at 24 months (39)
Anti IL-21 + liraglutide	Combination of an anti-IL-21 mAb and a GLP-1 receptor agonist	Anti-IL-21 provides transient immunomodulation by blocking IL-21, reducing $CD8^+$ T-cell trafficking to pancreatic islets Liraglutide improves beta-cell function	Phase2	Change in AUC of C-peptide secretion over a 4-hour MMTT at 54 weeks (40)
ATG	Rabbit antibodies against human thymocytes	Depletes T cells	Phase2b	AUC of stimulated C-peptide response over the first 2 hours of a 4-hour MMTT at 12 months (42)
Baricitinib	JAK1/JAK2 inhibitor	Probably acts on various cells including beta-cells and immune cells	Phase2	Mean AUC of C-peptide level during a 2-hour MMTT at 48 weeks (22)
Etanercept	Recombinant, soluble TNF receptor fusion protein	Blocks TNF	Phase2	Percentage change from baseline in HbA1c and C-peptide AUC at 24 weeks (44)
GAD-alum	Immunomodulatory antigen therapy	Induces immune tolerance, reduces autoimmune attack, preserves beta cell function	Phase2b	Endogenous insulin production (measured by C-peptide AUC) at 15 months (46)

Golimumab	Anti-TNF mAb	Blocks TNF	Phase2	Endogenous insulin production (measured by 4-hour C-peptide AUC) at 52 weeks (44)
Imatinib	Tyrosine kinase inhibitor	Probably acts on various cells including beta-cells and immune cells	Phase2	Mean AUC of stimulated C-peptide level over first 2 hours of a 4-hour MMTT at 12 months (49)
Rituximab	CD20-targeted mAb	Depletes B cells	Phase2	AUC of stimulated C-peptide response during first 2 hours of a 4-hour MMTT at 12 months (51)
Teplizumab	Anti-CD3 mAb	Targets CD3 on $CD8^+$ and $CD4^+$ T cells	Phase3	Change from baseline in β-cell function, as measured by stimulated C-peptide levels at 78 weeks (37)
Ustekinumab	IL-12/IL-23-targeted mAb	Neutralizes IL-12 and IL-23 by targeting the shared p40 subunit, modulating TH1 and TH17 responses	Phase2	AUC of C-peptide during a 2-hour MMTT at 52 weeks (54)
Verapamil	Calcium channel blocker that inhibits TXNIP	Reduces TXNIP expression and β-cell apoptosis	Phase3	AUC of C-peptide response following MMTT at 52 weeks (38)

Tableau 2 : Several therapies are being studied in recent onset stage 3 T1D

This table presents several therapies currently being studied for recent-onset stage 3 autoimmune T1D. It includes key details on each molecule, its description, mechanism of action, and primary endpoint.

3. Annexe 3 : Summary of the different studied molecules

Molecules	Description	Primary endpoints studied
Abatacept	Immunomodulators and immunosuppressants (CTLA4Ig)	**AUC of C-peptide** (39)
		Time to confirmed AGT tests result or stage 3 from randomization (32)
ATG	Immunomodulators and immunosuppressants (rabbit antibodies against human thymocytes)	**AUC of C-peptide** (42)
Rituximab	Immunomodulators and immunosuppressants (anti-CD20 mAb)	**AUC of C-peptide** (51)
Teplizumab	Immunomodulators and immunosuppressants (anti-CD3 mAb)	Change in β-cell function (by **C-peptide**) from baseline (37)
		Time to diagnosis of stage 3 T1D in high-risk relatives (24)
Anti-IL 21 + liraglutide	Cytokine Inhibitors (Blocking IL-21)	Change in **AUC of C-peptide** from baseline (40)
Etanercept	Cytokine Inhibitors (Anti-TNFα)	Change in **AUC of C-peptide** and HbA1c from baseline (44)
Golimumab	Cytokine Inhibitors (Anti-TNFα)	Endogenous insulin production (by **AUC of C-peptide**) (47)
Ustekinumab	Cytokine Inhibitors (Blocking IL-12 and IL-23)	Change in **AUC of C-peptide** from baseline (54)
Baricitinib	Intracellular pathway inhibitors (JAK1/JAK2 inhibitor)	**AUC of C-peptide** (22)
Imatinib	Intracellular Pathway Inhibitors (tyrosine kinase inhibitor)	**AUC of C-peptide** (49)
GAD-alum	Antigen-Specific Immunotherapy	Endogenous insulin production (by **AUC of C-peptide**) (46)
Verapamil	Calcium channel blocker that inhibits TXNIP	**AUC of C-peptide** (38)

Tableau 3 : Summary of the studied molecules

This table summarizes the molecules studied for T1D treatment, grouped by mechanism of action. The primary endpoints are listed, with C-peptide highlighted to reflect its common use in these studies.

BLANC Camille

NOUVELLES PERSPECTIVES DANS LA PRISE EN CHARGE DU DIABÈTE DE TYPE 1 : REVUE DE LITTÉRATURE SUR LA PRÉVENTION, LE DÉPISTAGE ET LES INNOVATIONS MÉDICAMENTEUSES

RÉSUMÉ

Introduction : Le diabète de type 1 (DT1) est une maladie auto-immune qui entraîne la destruction des cellules β, une dépendance à l'insuline à vie et des complications importantes. Cette revue explore les stratégies actuelles et émergentes de la prise en charge du DT1, en se concentrant sur la prévention, le dépistage précoce et les immunothérapies. Le DT1 progresse en plusieurs stades : stade 1, présence d'au moins deux auto-anticorps ; stade 2, dysfonctionnement des cellules β avec dysglycémie ; stade 3, diabète clinique caractérisé par une hyperglycémie.

Méthodes : Une revue de la littérature des publications scientifiques de 2015 à février 2025 a été réalisée sur PubMed et ClinicalTrials.gov. Les études ont été sélectionnées selon leur pertinence et de leur qualité méthodologique, en mettant l'accent sur le dépistage et les nouvelles cibles thérapeutiques. L'analyse met en évidence les avancées dans la prévention, le dépistage et les stratégies de traitement du DT1.

Résultats : Le dépistage précoce du DT1 à un stade pré-clinique permet de retarder son apparition grâce aux thérapies de modulation immunitaire. L'un des bénéfices immédiats est la réduction de l'incidence de l'acidocétose diabétique lors du diagnostic au stade 3 du DT1. Au total, 11 immunothérapies et 1 thérapie ont été examinées pour les formes présymptomatiques et récemment diagnostiquées.

Discussion : Le dépistage et l'intervention précoces améliorent les résultats à long terme et la qualité de vie des patients et de leurs familles. Cependant, des défis persistent dans la mise en œuvre du dépistage précoce, notamment l'absence de programme universel dans de nombreux pays, comme la France, malgré un consensus d'experts en faveur du dépistage des proches des personnes vivant avec le DT1. Le teplizumab reste la seule immunothérapie approuvée par la *Food and Drug Administration (FDA)* retardant l'apparition du stade 3. Concernant le stade 3, de nombreuses thérapies immunomodulatrices sont en développement clinique. Bien que l'aire sous la courbe du peptide-C soit un critère d'évaluation accepté, aucun consensus n'existe sur le seuil de bénéfice cliniquement significatif, ce qui représente un défi majeur pour l'approbation par la FDA. En somme, bien que des progrès significatifs aient été réalisés, la guérison du DT1 reste complexe.

Mots clés : autoanticorps, dépistage précoce, diabète de type 1, immunothérapie, peptide-C

NEW PERSPECTIVES IN THE CARE OF TYPE 1 DIABETES: A LITERATURE REVIEW OF PREVENTION, SCREENING AND PHARMACEUTICAL INNOVATIONS

ABSTRACT

Introduction: Type 1 diabetes (T1D) is an autoimmune disease that leads to β-cell destruction, lifelong insulin dependence, and significant health complications. This review explores current and emerging strategies for T1D management, focusing on prevention, early detection, and immunotherapies. Type 1 diabetes progresses through distinct stages: stage 1, presence of at least two autoantibodies; stage 2, β-cell dysfunction with dysglycemia; stage 3, clinical diabetes characterized by hyperglycemia.

Methods: A literature review of scientific publications from 2015 to February 2025 was conducted using PubMed and ClinicalTrials.gov. Studies were selected based on relevance and methodological quality, with a focus on screening and emerging therapeutic targets. The analysis highlights key developments in prevention, diagnosis, and treatment strategies for T1D.

Results: Early detection of T1D at preclinical stages offers significant benefits, including the opportunity to delay T1D onset with immune modulation therapies. One of immediate benefit is the reduced incidence of diabetic ketoacidosis at T1D stage 3 (the symptomatic stage) diagnosis. A total of 11 immunotherapies and 1 therapy were reviewed for presymptomatic and newly diagnosed T1D.

Discussion: Early screening and intervention prove long-term outcomes and quality of life for T1D patients and their families. Nevertheless, challenges in the implementation of early detection of T1D persist, including the lack of a universal screening program in many countries, such as France, despite expert consensus advocating for early screening for relatives of individuals living with T1D. Teplizumab remains the only immunotherapy approved by the Food and Drug Administration (FDA) for T1D, which delays the onset of stage 3 T1D. In the stage 3 indication, many immune modulatory therapies are currently in clinical development.

While C-peptide area under the curve is an accepted endpoint in these trials, no consensus exists on the threshold for clinically meaningful benefit, which represents a significant challenge for FDA approval. Overall, while significant progress has been made, the path to a cure for T1D remains challenging.

Keywords: autoantibodies, C-peptide, early screening, immunotherapy, type 1 diabetes