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Review

Innovative immunotherapies and emerging treatments in type 1 diabetes management

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ABSTRACT

Type 1 diabetes mellitus (T1D) is a chronic autoimmune disease characterized by the selective destruction of pancreatic insulin-producing beta cells, primarily mediated by CD4+ and CD8+ T cells. This review comprehensively examines the latest advances in immunotherapeutic approaches to T1D, categorizing current strategies into four main groups: antigen-independent therapies, antigen-dependent therapies, beta cell therapies, and stem cell therapies. Antigen-independent strategies, such as antibody-based therapies (e.g., Abatacept and Teplizumab) and cytokine inhibitors (e.g., Anakinra and Etanercept), have shown potential in preserving beta cell function by modulating immune responses. Antigen-dependent strategies focus on inducing immune tolerance to specific beta cell antigens, with mixed results from clinical trials involving autoantigen vaccines like GAD65. Beta cell therapies, including islet transplantation, offer promising outcomes but face challenges related to immunosuppression and donor availability. Stem cell therapies, particularly using mesenchymal stem cells (MSCs) and autologous hematopoietic stem cells (HSCs), demonstrate potential in immune modulation and beta cell regeneration. Novel approaches, such as Chimeric Antigen Receptor (CAR)–Tregs therapy and JAK-STAT pathway inhibition, represent exciting areas of ongoing research. This comprehensive overview underscores the necessity of personalized therapeutic approaches and continued research to optimize existing therapies and explore new targets, ultimately aiming to improve outcomes and achieve a potential cure for T1D.

1. Introduction

Type 1 Diabetes (T1D) is a chronic autoimmune disorder characterized by the selective destruction of pancreatic insulin-producing beta cells by the immune system. The pathogenesis of T1D primarily involves autoreactive CD4+ and CD8+ T cells, which orchestrate an autoimmune attack through both innate and adaptive immune mechanisms. CD8+ cytotoxic T lymphocytes are directly responsible for beta cell destruction, while CD4+ helper T cells facilitate and amplify this autoimmune response. B cells and the autoantibodies they produce also contribute to the pathophysiology of T1D, serving as both mediators of beta cell destruction and biomarkers for disease progression [1–3].

The progression of T1D typically occurs in three stages. The initial stage is marked by the presence of islet-specific autoantibodies, detectable long before the clinical onset of the disease. These autoantibodies target beta cell antigens such as insulin, glutamic acid decarboxylase (GAD65), and islet antigen-2 (IA-2). The second stage is characterized by a gradual decline in beta cell mass and function, leading to impaired glucose tolerance and, ultimately, the development of overt diabetes. In the final stage, patients require lifelong insulin therapy to maintain glucose homeostasis and prevent complications [1,2,4]. Recent advances in immunotherapy have opened new avenues for treating T1D, focusing on modulating the immune response to preserve beta cell function and delay or prevent disease onset. This review provides a comprehensive overview of these immunotherapeutic strategies, categorizing current approaches into four main groups: antigen-independent therapies, antigen-dependent therapies, beta cell therapies, and stem cell therapies. Additionally, we highlight emerging novel strategies that are currently under investigation, offering insights into the future of T1D management (Fig. 1).

2. Antigen-independent strategies

Antigen-independent strategies include antibody-based therapies, proinflammatory cytokine-based therapies, and T regulatory cells (Tregs)-mediated therapies.

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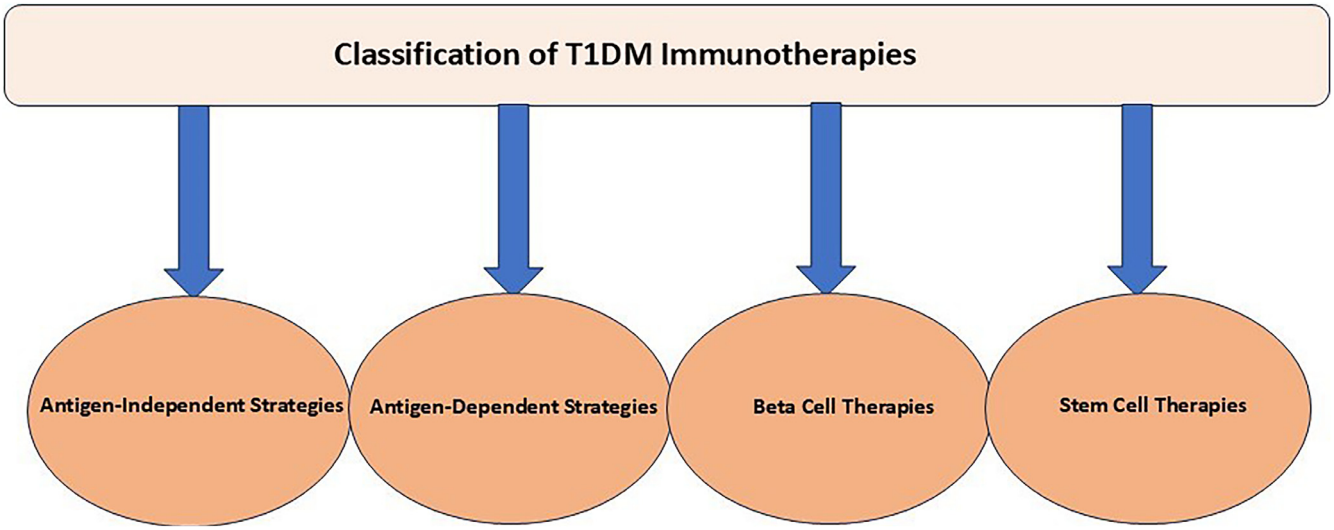

Fig. 1. Classification of Type 1 Diabetes Immunotherapies. The figure categorizes the current immunotherapeutic strategies for Type 1 Diabetes into four main approaches: Antigen-Independent Strategies, Antigen-Dependent Strategies, Beta Cell Therapies, and Stem Cell Therapies.

2.1. Antibody-based therapies

Antibody-based therapies target various immune checkpoints and pathways involved in the autoimmune response against beta cells. One such approach involves the use of monoclonal antibodies to block immune checkpoints like PD-1, CTLA-4, and LAG-3, which are critical regulators of T cell activity. By inhibiting these checkpoints, these therapies aim to reduce the activation and proliferation of autoreactive T cells that attack pancreatic beta cells [5,6]. These therapies offer targeted immunomodulation, allowing for the selective suppression of pathogenic immune responses while preserving overall immune function. This specificity reduces the risk of broad immunosuppression and associated complications. Additionally, these therapies have the potential to modify the course of T1D by preserving residual beta-cell function and delaying disease progression. This can lead to prolonged periods of insulin independence or reduced insulin requirements, significantly improving patients' quality of life [5]

Several antibodies have shown efficacy in T1D treatment. Notable examples include Abatacept, an anti-CTLA4 antibody currently under investigation (NCT01773707). Studies have shown that Abatacept can delay the loss of beta-cell function in recent-onset T1D. In a randomized controlled trial, Abatacept-treated patients exhibited a slower decline in C-peptide levels compared to the placebo group, indicating preservation of beta-cell function [7–9]. Teplizumab and Otelixizumab, anti-CD3 monoclonal antibodies have demonstrated promise in clinical trials. Teplizumab (recently approved by FDA to delay type 1 diabetes onset) has been shown to delay the onset of T1D in high-risk individuals by modulating T cell responses. A study published recently revealed that Teplizumab treatment delayed the median time to diagnosis by approximately two years compared to the placebo group [9,10].

Despite their advantages, antibody-based therapies come with several challenges. Immune checkpoint inhibitors can lead to immune-related adverse events (irAEs) due to the broad activation of the immune system. These adverse effects can range from mild to severe and may affect various organs, necessitating careful monitoring and management. The efficacy of these therapies can also vary among individuals due to differences in genetic background, disease stage, and individual immune profiles, which necessitates personalized approaches to therapy. Additionally, these therapies are often expensive, limiting accessibility for many patients. The high cost of monoclonal antibodies and the need for specialized care and monitoring can pose significant barriers to widespread use [5,6,11].

2.2. Proinflammatory cytokine-based therapies

Proinflammatory cytokines contribute significantly to the recruitment and activation of immune cells within pancreatic islets, exacerbating the autoimmune response. By targeting these cytokines, therapies aim to reduce inflammation and preserve beta-cell function. For example, monoclonal antibodies that neutralize TNF-α can modulate immune responses in T1D by reducing the inflammatory environment in the pancreas, thereby protecting beta cells from immune-mediated damage [12,13]. Anakinra, an IL-1 receptor antagonist, has shown promise in reducing inflammation and preserving beta-cell function. Clinical trials have demonstrated its potential to improve glycemic control and reduce HbA1c levels in patients with T1D [14,15]. Canakinumab, another IL-1β inhibitor, has shown similar benefits. Both therapies require careful monitoring for infections and other adverse effects [16,17]. TNF-α blockers such as Etanercept and Infliximab, commonly used in other autoimmune conditions, are also being explored for T1D. These agents can reduce systemic inflammation and have shown preliminary efficacy in preserving beta-cell function. However, their use is associated with an increased risk of infections and other immune-related side effects [18–20]. In addition, IL-6 inhibitors like Tocilizumab, are being investigated for their potential in T1D. IL-6 is involved in the inflammatory response and has been implicated in the pathogenesis of several autoimmune diseases. Recent studies suggest that Tocilizumab can reduce systemic inflammation and may help preserve beta-cell function in T1D. however, some experiments indicated that the inhibition of IL-6 receptor could not decrease β cell destruction in new-onset T1DM [21,22]. Ongoing clinical trials aim to evaluate its efficacy and safety in this specific context. Although primarily an anti-CD3 antibody, teplizumab affects IL-21, a cytokine involved in the survival and function of T cells. By modulating IL-21 levels, teplizumab may indirectly contribute to reducing the autoimmune attack on beta cells [13,23]. Ongoing clinical trials continue to investigate the efficacy and safety of various cytokine inhibitors in T1D. Research is also focusing on identifying biomarkers to predict treatment response, which could lead to more personalized approaches. Combining cytokine inhibitors with other immunomodulatory or regenerative therapies holds promise for enhancing overall treatment efficacy and improving

outcomes for patients with T1D [24,25]. Despite their advantages, proinflammatory cytokine-based therapies have several disadvantages. One significant challenge is the risk of adverse effects. While targeted, cytokine inhibitors can lead to significant adverse effects, including an increased risk of infections due to their role in modulating the immune system. The efficacy of cytokine inhibitors can also vary among individuals due to differences in genetic background, disease stage, and individual immune profiles, necessitating personalized treatment approaches. Additionally, the development and production of monoclonal antibodies and other biologics are costly, which can limit accessibility for many patients. The high cost of these therapies, combined with the need for ongoing treatment and monitoring, poses a significant barrier to widespread use [26–28].

2.3. Tregs-mediated therapies

These therapies aim to expand Tregs to increase immune tolerance. Tregs, or regulatory T cells, are a subset of T cells that play a crucial role in maintaining immune system balance and preventing autoimmune diseases. Various studies of Tregs in T1DM suggest that their dysfunction contributes to disease pathogenesis. Although Treg numbers in peripheral blood typically remain unchanged, their suppressive function is frequently diminished [29–31], and their gene expression profile is altered [32]. Impaired IL-2 signaling, evidenced by reduced IL-2-stimulated phosphorylation of signal transducer and activator of transcription 5 (STAT5), increased expression of protein tyrosine phosphatase N2 (PTPN2), and a negative regulator of IL-2 signaling, contributes to these changes [33,34]. SNPs in regions important for Treg identity have also been identified [12]. Direct evidence connecting Treg dysfunction to T1DM is provided by studies on IPEX syndrome, where FOXP3 mutations lead to Treg dysfunction and autoimmunity, often including T1DM [35]. A study on IPEX syndrome provided significant evidence of the connection between Treg dysfunction and type 1 diabetes, showing that FOXP3 mutations cause varying degrees of Treg dysfunction and multiorgan autoimmunity, often including type 1 diabetes [35]. Several trials of Treg administration in newly diagnosed T1DM have shown the therapy to be safe and well-tolerated [36–38]. A recent study demonstrated that low-dose IL-2 therapy selectively expands Tregs and preserves beta cell function in new-onset T1D patients [39] . In a phase I trial, low-dose IL-2 treatment led to an increase in Treg numbers and stabilization of C-peptide levels, suggesting a potential benefit in T1D management [36]. Similarly, Marek-Trzonkowska et al. showed that children who received Treg therapy maintained higher C-peptide levels and required less insulin one year after treatment compared to a matched control group [38]. Although there were no significant improvements in disease severity, Bluestone et al. found that C-peptide levels were maintained for over two years after treatment in some patients [37]. Despite these findings, enhancing Treg function, survival, and proliferation in vivo by adding low-dose IL-2 to Treg therapy can increase Treg numbers. However, it may also expand inflammatory cell subsets, making it a less ideal approach [36]. These results are consistent with other trials of polyclonal Treg therapy in different diseases, showing excellent safety but undetermined efficacy [40]. Therefore, a variety of novel genetic engineering approaches are needed to enhance the therapeutic efficacy of Treg therapy.

Building on these traditional approaches, Chimeric Antigen Receptor (CAR)-Tregs therapy represents a more advanced and targeted strategy. CAR-Tregs are genetically engineered to express chimeric antigen receptors that can specifically recognize and bind to antigens on pancreatic beta cells. This method involves the genetic engineering of regulatory T cells (Tregs) to express chimeric antigen receptors (CARs), enabling these cells to specifically target and suppress autoimmune responses against pancreatic β-cells [41,42].

One of the primary advantages of CAR-Tregs therapy is its ability to provide targeted immunomodulation. This therapy specifically targets the autoimmune cells responsible for beta-cell destruction, potentially reducing the risk of widespread immunosuppression [43]. Additionally, research suggests that CAR-Tregs can induce long-lasting remission in T1D patients by promoting immune tolerance [44]. The personalized nature of this therapy allows for its tailoring to individual patients, thereby enhancing its efficacy and minimizing adverse effects [45]. Clinical trials have shown encouraging results, with CAR-Tregs reducing the need for exogenous insulin by preserving or restoring beta-cell function. [38].

Despite these notable advantages, CAR-Tregs therapy also faces significant challenges. The complexity and cost associated with the manufacturing and administration of CAR-Tregs can limit their accessibility [46]. There are also safety concerns related to the genetic modifications involved and the potential for off-target effects, which could lead to adverse reactions [47]. The efficacy of CAR-Tregs therapy can vary among patients due to individual differences in immune system dynamics and disease progression [48]. Furthermore, stringent regulatory requirements for gene therapies can slow down the clinical translation and widespread adoption of CAR-Tregs therapy [49].

Recent research and clinical trials have provided valuable insights into the potential and challenges of CAR-Tregs therapy for T1D. For example, Bluestone et al. conducted a study demonstrating that CAR-Tregs could maintain immune homeostasis and prevent beta-cell destruction in a mouse model of T1D [50] . Fraser et al. reviewed the potential for CAR-Tregs in personalized medicine, highlighting the customization of CAR constructs to enhance specificity and safety [51]. Wright et al. provided evidence from a phase I clinical trial where T1D patients treated with CAR-Tregs showed improved beta-cell function and reduced insulin requirements. Grupp et al. (2021) discussed the safety profile of CAR-Tregs, emphasizing the need for rigorous monitoring and management of potential adverse effects [52,53]. The key Antigen-Independent Immunotherapeutic Strategies discussed above are summarized in Table 1, providing an overview of their therapeutic approaches, mechanisms of action, examples, and associated challenges.

In conclusion, Tregs-mediated therapies, encompassing both traditional and CAR-Tregs approaches, offer promising avenues for the treatment of T1D by enhancing immune regulation and protecting

Table 1
Antigen-Independent Immunotherapeutic Strategies in Type 1 Diabetes

Strategy Type	Therapeutic Approach	Mechanism of Action	Key Examples	Challenges	References
Antibody-Based Therapies	Blocking immune checkpoints	Inhibits T cell activation and proliferation	Abatacept, Teplizumab, Otelixizumab	Immune-related adverse events, high cost, variable efficacy	[5,7–9]
Proinflammatory Cytokine-Based Therapies	Neutralizing cytokines involved in inflammation	Reduces inflammation and protects beta cells	Anakinra, Canakinumab, Tocilizumab	Risk of infections, variability in patient response	[14,16,21]
Tregs-Mediated Therapies	Expanding Tregs to enhance immune tolerance	Enhances immune regulation and suppresses autoimmunity	Low-dose IL-2, Polyclonal Treg therapy	Inconsistent efficacy, potential for expanding inflammatory cell subsets	[36,39,41,42,47]

beta cells. While traditional therapies focus on expanding and enhancing Tregs function, CAR-Tregs provide a more targeted approach that could potentially achieve greater efficacy. Ongoing research and clinical trials are essential to overcoming the challenges associated with these therapies and bringing them closer to clinical application.

3. Antigen-dependent strategies

Antigen-dependent strategies focus on the specific modulation of T1D-related autoimmunity without affecting normal immune homeostasis.

3.1. Autoantigen-based therapies in T1D: vaccination and treatment approaches

T1DM involves various immune dysfunctions, such as low autologous lymphocyte response, high plasma IFN-γ and TNF-α levels [54,55], and defects in T helper cell function [56] and suppressor cell activity [57,58], along with Defective antigen presenting cells (APC) [59]. Vaccines that can address these immune issues may help prevent β-cell autoimmunity. Studies in Non-Obese Diabetic (NOD) mice have shown that APC-activating vaccines (e.g., streptococcal-derived preparations, Bacillus Calmette-Guerin (BCG), mycobacterium avium intracellulare, and bee venom) can prevent diabetes by boosting regulatory T cells and/or Th2 responses [60].

Despite identifying several β-cell antigens like (pro)insulin [61], GAD [62], and IA-2 [63,64], the primary target antigen remains unknown. Effective vaccines need to regulate autoimmunity without affecting overall immune function, exploring various administration routes like inhaled, nasal, oral, and modified antigens for improved tolerance [65]. Intraperitoneal proinsulin peptides and subcutaneous insulin B chain peptide B:9-23 have shown efficacy in NOD mice [66,67], leading to human trials, though no successful outcomes have been reported yet [68–71]. GAD-based vaccines have also shown promise in preclinical studies but face challenges in human trials [72]. Combining anti-IL-1β antibody with a GAD65 vaccine showed a 33% disease reversal in a virus-induced mouse model [73], suggesting potential when used together. Different administration routes for GAD DNA vaccines were tested, with intradermal and oral routes proving more effective than intramuscular delivery in NOD mice [74]. however, A meta-analysis of clinical trials involving GAD65 vaccination indicated a modest but significant preservation of beta cell function in newly diagnosed T1D patients (62, 63).

BCG, a long-used tuberculosis vaccine, has shown promise in T1DM, reducing HbA1c levels in long-term patients over five years [75]. BCG works by stimulating TNF production, which targets autoimmune cells [76,77]. Diabetic patients are more prone to infections, which can exacerbate complications [78]. Viruses like Coxsackievirus B (CVB) and Rotavirus (RV) have been linked to T1DM, with CVB1 vaccines protecting against diabetes in preclinical studies [79,80]. Enteroviruses (EVs) are significant triggers for islet autoimmunity, with EV vaccines potentially protecting against T1DM [81]. Initial studies may focus on high-risk infants identified by HLA genotyping [82]. Given the diversity of viruses that can initiate autoimmunity, a single-virus vaccine may not be sufficient [60].

Autoantigen treatment is an innovative approach in T1D therapy aimed at reducing or halting the autoimmune response by administering autoantigens against which the autoimmune process develops. This strategy seeks to induce immune tolerance and preserve the insulin-producing beta cells, which are the primary target in T1D.

Recent clinical trials have explored various autoantigen treatments with varying degrees of success. One significant study involved IMCY-0098, a peptide derived from human proinsulin, administered to patients with recent-onset T1D. This first-in-human phase 1b study demonstrated that IMCY-0098 was safe and showed potential in modifying the immune response in T1D patients, although further trials are needed to confirm its efficacy in preserving beta-cell function [83].

Another notable approach is the use of GAD-alum (Diamyd). A phase 2b trial, DIAGNODE-2, investigated the intralymphatic administration of GAD-alum in combination with oral vitamin D in T1D patients carrying the HLA DR3-DQ2 haplotype. The results indicated that this treatment improved glycemic control and preserved beta-cell function in the genetically susceptible subgroup of patients, highlighting the importance of personalized medicine in T1D treatment [84].

Advantages of autoantigen treatment include its specificity and the potential for fewer side effects compared to broad-spectrum immunosuppressive therapies. By targeting the autoimmune process directly, these treatments can preserve residual beta-cell function, improve glycemic control, and reduce the need for exogenous insulin. Additionally, such therapies can be tailored to individuals based on their genetic makeup, enhancing their efficacy and minimizing adverse effects.

However, there are disadvantages to consider. The efficacy of autoantigen treatments can be inconsistent, as seen in various trials where some treatments did not meet their primary endpoints. This inconsistency highlights the challenge of addressing the heterogeneous nature of T1D. Furthermore, the long-term effects and durability of these treatments remain uncertain, requiring extensive follow-up studies. There is also the risk of incomplete tolerance induction, where the immune system might continue to attack beta cells despite treatment [85].

In summary, autoantigen-based therapies, encompassing both vaccination and treatment approaches, represent encouraging but still developing strategies in the management of T1D. They offer targeted approaches that could significantly improve patient outcomes by preserving beta-cell function and reducing autoimmune attacks. Continued research and well-designed clinical trials are crucial to fully realize their potential and address current limitations.

3.2. Inhibition of specific autoantigen B cells

Given the limited success of non-specific B cell elimination, targeting specific autoantigen B cells presents a compelling alternative. A study using Rituximab, an anti-CD20 antibody, showed transient preservation of beta cell function in newly diagnosed T1D patients. In a randomized controlled trial, Rituximab-treated patients exhibited higher C-peptide levels compared to the placebo group after one year, indicating a delay in disease progression [86]. Another study discussed the combination of Rituximab with proinsulin DNA vaccine in NOD mice, which aimed to induce immune tolerance. The study showed that this combination could enhance the regulatory T cell function and reduce the effector cell load, offering synergistic protection against T1D. This suggests potential for combination therapies in enhancing the efficacy of Rituximab in clinical settings [87]. An experiment provided a two-year follow-up on the effects of B-lymphocyte depletion using Rituximab. The study confirmed that while Rituximab slowed the decline of beta-cell function in the first year, the effect did not persist long-term, with B-lymphocyte levels returning to baseline by 18 months. This highlights the need for additional or combination therapies to sustain the benefits [86].

4. Beta cell therapies

4.1. Islet transplantation

Islet transplantation has emerged as a prominent treatment for T1D, aiming to restore endogenous insulin production by transplanting insulin-producing islets from a donor pancreas into a patient.

[88]. Recent clinical trials and meta-analyses have provided valuable insights into the efficacy and challenges of this approach.

One of the primary advantages of islet transplantation is improved glycemic control. Islet transplantation can significantly enhance glycemic control, reducing HbA1c levels (hemoglobin A1c <7%) and minimizing glucose variability [89]. Patients often experience fewer hypoglycemic episodes, contributing to a better quality of life [90]. Additionally, the procedure reduces the frequency and severity of hypoglycemic events, which are common and dangerous in T1D patients [91]. This reduction is particularly beneficial for those who have hypoglycemia unawareness. Moreover, some patients achieve insulin independence post-transplantation, though this is more likely in the short term. Approximately 44% of patients remain insulin-independent after three years, showcasing the potential for durable treatment effects [92]. Nevertheless, long-term research has revealed varying outcomes. Studies have demonstrated that sustained insulin independence is rare, with only 32% of patients remaining insulin-independent after 5 years and just 8% after 20 years (islet transplantation1). Despite this, insulin requirements significantly decreased, averaging 20-30% of baseline levels throughout the follow-up period [93].

However, the method is not without its disadvantages. Long-term immunosuppressive therapy is required to prevent graft rejection, which can have serious side effects, including increased risk of infections and malignancies [94]. These adverse effects pose a significant barrier to widespread adoption. Additionally, the long-term success of islet transplantation is variable, with many patients experiencing a gradual decline in graft function over time [90]. Factors influencing this include the quality of the islet preparation and the patient's immune response. Another major challenge is the limited availability of donor islets, making it difficult to meet the demand for transplantation [95]. This scarcity necessitates ongoing research into alternative sources such as xenotransplantation and stem cell-derived islets.

Recent research has focused on improving outcomes and reducing complications. For instance, novel immunosuppressive protocols are being developed to minimize side effects while effectively preventing rejection [89]. For instance, the combined administration of anakinra and etanercept, along with a high BETA-2 score within the first year following the initial islet infusion, has been indicators of long-term graft survival [93]. Additionally, advancements in islet isolation and preservation techniques are being explored to enhance the viability and functionality of transplanted islets [96].

In conclusion, while islet transplantation significantly reduces severe hypoglycemia and insulin requirements, it has limited success in achieving long-term insulin independence and glycemic control. Future advances in β-cell replacement therapy and immune response management are essential for improving the outcomes and viability of islet transplantation as a treatment for type 1 diabetes. Ongoing research and clinical trials are essential to overcome these obstacles and make this treatment more widely accessible.

5. Stem cell therapies

5.1. Autologous hematopoietic stem cells (HSCs)

Autologous Hematopoietic Stem Cell (HSC) transplantation has emerged as a potential therapeutic approach for type 1 diabetes (T1D). This method leverages the patient's own HSCs to reset the immune system, potentially halting the autoimmune attack on pancreatic beta cells and preserving their function.

HSCs have shown promise in treating blood cancers and possess significant immunoregulatory capabilities, making them valuable in addressing immune-related diseases such as T1D, multiple sclerosis (MS), systemic sclerosis, systemic lupus erythematosus, and Crohn's disease. Although HSCs are scarce in healthy individuals, they can effectively modulate immune responses [97,98].

The primary advantage of autologous HSC transplantation is its ability to reset the immune system, significantly reducing autoimmune attacks on beta cells. This can lead to the preservation and partial recovery of beta-cell function, potentially reducing or eliminating the need for exogenous insulin. Recent studies have demonstrated these benefits, highlighting the potential of HSC transplantation in achieving prolonged insulin independence and improved metabolic control [99–101].

The NOD mouse model, which naturally develops autoimmune diabetes, has been instrumental in exploring HSC-based interventions. Two primary methods have been investigated: infusing HSCs to create mixed chimerism and genetically modifying HSCs to alter the immune system. These methods have been successful in preventing diabetes in NOD mice, but their application in humans is constrained by the necessity for myeloablative treatments [99].

Autologous HSC transplantation has been used in clinical trials for autoimmune diseases, including T1D. Significant insulin independence and well-preserved glycometabolic control have been observed in Autologous HSC transplantation -treated T1D patients [102–105]. However, long-term follow-up shows variability in outcomes, with some patients experiencing relapse while others remain insulin-independent for years [105–107]. The effectiveness of Autologous HSC transplantation appears influenced by patients' immune profiles, suggesting a need for personalized approaches [102,105,108].

However, the process of harvesting, conditioning, and re-infusing HSCs is complex, requiring specialized medical facilities and experienced healthcare providers. This complexity increases the cost and limits the accessibility of the treatment. Detailed procedures and the associated challenges are outlined in clinical trials and reviews [109]. A critical step in the procedure is immunosuppression, which can lead to significant side effects, including infections and other complications. The reconstitution of the immune system post-transplantation also poses risks that are not yet fully understood. These concerns are highlighted in reviews which call for more extensive research to fully understand these risks [110]. Additionally, patient outcomes can vary significantly due to factors such as age, disease duration, and specifics of the HSC transplantation protocol. This variability makes it challenging to predict individual patient responses and complicates the standardization of the treatment [102]. In conclusion, autologous HSC transplantation holds significant promise for improving the management of T1D by modulating the immune system and preserving beta-cell function. However, the procedure's complexity, potential risks, and the need for more long-term studies temper its immediate application in widespread clinical practice. Ongoing research aims to optimize protocols and enhance our understanding of this innovative treatment approach.

5.2. Mesenchymal stem cells (MSCs)

Mesenchymal Stem Cells (MSCs) have emerged as a potential therapeutic option for the treatment of type 1 diabetes T1D. These multipotent stromal cells, capable of differentiating into a variety of cell types including bone, cartilage, and fat cells, have shown significant promise in regenerative medicine due to their immunomodulatory properties and ability to support tissue repair and regeneration. One of the key advantages of MSCs in the treatment of T1D is their strong immunomodulatory effects. MSCs can suppress the immune system's attack on pancreatic beta cells, which is crucial in an autoimmune condition like T1D. By modulating the immune response, MSCs reduce inflammation and create a more favorable environment for beta cell survival. This ability to alter immune function has been demonstrated in various studies, showing that MSCs can help preserve and potentially restore beta-cell function [110]. In addition to their immunomodulatory properties, MSCs also contribute to tissue repair and regeneration. MSCs can home to sites of injury and support the

repair of pancreatic islets, enhancing their function. For example, MSCs have been shown to enhance islet graft vascularization, which is critical for the survival and functionality of transplanted islets [110]. This capacity for tissue repair highlights the therapeutic potential of MSCs beyond merely modulating the immune response. Despite these encouraging benefits, the efficacy of MSC therapy can be inconsistent, with patient responses varying due to differences in MSC sources, dosage, and individual patient factors. This variability complicates the standardization of MSC therapies and underscores the need for more research to optimize treatment protocols [111]. Moreover, while short-term results are encouraging, there is a lack of long-term data on the durability and sustained efficacy of MSC treatments for T1D. Extensive and longer-term studies are needed to fully understand the potential and limitations of MSC therapy [110]. The process of isolating, expanding, and administering MSCs is complex and requires specialized facilities and expertise, increasing the cost and limiting accessibility. This complexity, along with the associated challenges, is well-documented in clinical trials and reviews [109].

Recent clinical trials have provided valuable insights into the potential of MSCs in treating T1D. For instance, Hu et al. reported that patients receiving MSCs derived from Wharton's Jelly showed an increase in C-peptide levels and a decrease in insulin requirements compared to controls [112]. Similarly, Carlsson et al. used autologous bone marrow-derived MSCs in T1D patients, reporting improved C-peptide responses and reduced insulin needs after one year [113]. Furthermore, a systematic review and meta-analysis by He et al. found that MSC infusion improved HbA1c levels, although there were no significant differences in fasting glucose or C-peptide levels [114].

To conclude, MSC therapy represents a valuable avenue for the treatment of T1D, offering potential benefits through immunomodulation and tissue repair. However, challenges such as variable efficacy, limited long-term data, and the complexity of treatment must be addressed through ongoing research and clinical trials to fully realize the potential of MSCs in managing and potentially curing T1D.

6. Novel immunotherapeutic strategies

6.1. JAK-STAT pathway inhibition

The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway is crucial for various cellular processes, including immunity, cell division, and survival. Recent research has investigated the inhibition of the JAK-STAT pathway as a potential therapeutic approach for managing T1D. This pathway is integral to immune cell function, mediating responses to cytokines such as interleukins, interferons, and growth factors. Dysregulation of the JAK-STAT pathway can lead to autoimmune responses, making it a target for therapeutic intervention in T1D [115].

In T1D, the immune system erroneously targets and destroys insulin-producing beta cells in the pancreas. The JAK-STAT pathway is often hyperactivated in autoimmune conditions, contributing to the chronic inflammation and immune dysregulation seen in T1D [116]. This hyperactivation leads to increased production of pro-inflammatory cytokines, exacerbating the autoimmune response.

JAK inhibitors, or JAKinibs, have been developed to mitigate the aberrant signaling observed in autoimmune diseases, including T1D. These small molecules selectively inhibit one or more JAK isoforms, reducing the inflammatory response. Recent studies have explored their potential in T1D management. For instance, tofacitinib, an oral JAK inhibitor targeting JAK1 and JAK3, is primarily used for rheumatoid arthritis and ulcerative colitis, but its potential in T1D is under investigation. Preliminary studies suggest that [117].

Another noteworthy JAK inhibitor is baricitinib, a selective inhibitor of JAK1 and JAK2, which has shown effectiveness in rheumatoid arthritis. A clinical trial in T1D patients demonstrated that baricitinib could reduce the autoimmune attack on beta cells and improve metabolic parameters [118]. Additionally, ruxolitinib, targeting JAK1 and JAK2, has shown promise in conditions like myelofibrosis and is being explored for its efficacy in T1D. Early-phase trials indicate it might help modulate immune responses in T1D [119,120].

The use of JAK inhibitors offers several advantages. These drugs provide targeted action, modulating multiple cytokine pathways simultaneously, which can lead to significant clinical improvement and reduction in disease activity They also offer the convenience of oral administration compared to biologics, which often require injections [121].

However, there are potential disadvantages and risks associated with JAK inhibition. These include increased susceptibility to infections, potential malignancy risk, and adverse events such as gastrointestinal perforations and blood clots. Long-term safety data are still being accumulated, necessitating cautious use and thorough patient monitoring [122]. Moreover, the variability in patient responses due to genetic and environmental factors can affect the efficacy of JAK inhibitors [123,124].

In conclusion, while JAK-STAT pathway inhibition represents a viable strategy for managing T1D by modulating immune responses and reducing inflammation, further research and clinical trials are necessary to fully understand its benefits and risks. The development of JAK inhibitors offers new therapeutic options, but their application must be approached with caution, considering individual patient variability and potential side effects.

6.2. Beta cell preservation

Alpha-1 Antitrypsin (AAT) has emerged as a significant therapeutic candidate for preserving beta cells in T1D. This protein, traditionally known for its role in protecting tissues from enzyme damage, also exhibits significant anti-inflammatory and immunomodulatory properties. Recent clinical trials and studies have explored its efficacy in T1D, particularly focusing on its ability to preserve insulin-producing beta cells.

One notable study involved a phase II, double-blind, randomized, placebo-controlled, multicenter trial that assessed the efficacy, safety, and tolerability of AAT (Glassia) in patients with recent-onset T1D. Seventy patients were treated with either 60 mg/kg or 120 mg/kg AAT or placebo over a year. The primary endpoint was the change in C-peptide area under the curve (AUC) from a 2-hour mixed-meal tolerance test (MMTT) after 52 weeks. The results indicated that the higher dose of AAT (120 mg/kg) maintained higher C-peptide levels compared to placebo, suggesting a protective effect on beta cells, although the differences were not statistically significant overall. However, in a subgroup of adolescents, AAT showed more inspiring results, maintaining better C-peptide levels and achieving lower HbA1c levels compared to the placebo group [83].

The advantages of AAT therapy include its dual role in reducing inflammation and modulating immune responses, which is crucial in the context of autoimmune diseases like T1D. By curbing the inflammatory responses and promoting beta cell survival, AAT can potentially slow down disease progression and preserve residual insulin production. This can translate into better metabolic control and reduced insulin requirements for patients [125].

However, there are also disadvantages to consider. The primary concern is the need for frequent and possibly lifelong administration, which can be burdensome for patients. Additionally, the cost of AAT therapy can be high, potentially limiting its accessibility. While the safety profile of AAT is generally favorable, with minimal adverse effects reported, long-term safety data are still needed to fully understand the implications of chronic AAT use [126].

In summary, AAT therapy holds promise as a method for beta cell preservation in T1D, particularly in newly diagnosed patients. The ability of AAT to modulate immune responses and reduce inflammation provides a novel approach to managing T1D, potentially

Table 2
Novel Immunotherapeutic Strategies in Type 1 Diabetes

Therapy Type	Mechanism of Action	Key Advantages	Challenges	References
JAK-STAT Pathway Inhibition	Inhibition of the JAK-STAT signaling pathway to reduce autoimmune activity.	Targeted action, convenient oral administration.	Increased infection risk, potential for severe side effects.	[116,118,119,122–124]
Beta Cell Preservation (AAT Therapy)	Reducing inflammation and modulating immune responses to preserve beta cells.	Dual role in reducing inflammation and promoting beta cell survival.	Need for frequent administration, high cost.	[83,125,126]
Metabolic Targeting (GLUT1 Inhibition)	Inhibiting GLUT1 to reduce glycolysis in autoreactive T cells, decreasing their activity.	High selectivity, targeted immunomodulation.	Potential off-target effects, long-term safety concerns.	[127–129]
SASP Modulation for Beta Cell Preservation	Targeting the senescence-associated secretory phenotype to reduce local inflammation.	Slows beta cell destruction, preserves residual beta cell function.	Complexity in designing therapies, risk of unintended side effects.	[130–134]

improving patient outcomes. Further studies and long-term clinical trials are warranted to better define its efficacy and safety profile, as well as to optimize dosing regimens and identify the most responsive patient populations [83,125].

6.3. Metabolic targeting in T1D

Metabolic targeting of autoreactive T cells via GLUT1 inhibition represents a potential strategy to control T1D. GLUT1, a critical glucose transporter, is overexpressed in activated T cells, including those involved in the autoimmune response in T1D. Small molecules such as STF-31, WZB117, and BAY-876 have shown potential in selectively inhibiting GLUT1, thereby reducing glucose uptake and metabolic activity in these T cells, which dampens their pathological activity [127].

The advantages of this approach lie in its selectivity and efficacy. BAY-876, for instance, is highly selective for GLUT1, demonstrating significant inhibition with minimal impact on other GLUT isoforms. This specificity reduces off-target effects and enhances the therapeutic potential for autoimmune conditions like T1D [128]. Moreover, targeting GLUT1 impairs glycolysis specifically in autoreactive T cells, which rely heavily on glucose metabolism for their proliferation and function. This metabolic reprogramming can reduce the autoimmune attack on pancreatic beta cells without broadly suppressing the immune system, thereby offering a more targeted immunomodulation [127].

However, the potential toxicity of this method cannot be overlooked. GLUT1 is also expressed in various non-immune cells, including those in the brain and red blood cells. Inhibition of GLUT1 can lead to off-target effects, potentially causing adverse outcomes such as hypoglycemia and neurotoxicity [129]. Furthermore, the long-term safety of chronic GLUT1 inhibition remains uncertain. There are concerns about metabolic adaptations and the potential development of resistance or compensatory mechanisms in other glucose transporters, which could undermine the treatment's efficacy over time [128].

Recent studies have highlighted the efficacy of these inhibitors in preclinical models. For example, STF-31 and WZB117 have been shown to effectively reduce glycolytic flux in activated T cells, thereby mitigating their pathogenic activity in autoimmune diabetes models [127]. Despite these encouraging results, further research, including clinical trials, is essential to validate these findings and address the associated safety concerns comprehensively. While the advantages of selectivity and targeted action are evident, potential risks related to off-target effects and long-term safety necessitate careful clinical evaluation. Continued research and clinical trials will be crucial to determine the viability of this approach for widespread therapeutic use in T1D patients [127].

6.4. Modulating the senescence-associated secretory phenotype (SASP) to preserve beta cells in T1D

Beta cells play a crucial role in the pathology of T1D, particularly through mechanisms such as the senescence-associated secretory phenotype (SASP). SASP is characterized by the secretion of a wide array of pro-inflammatory cytokines, chemokines, proteases, and growth factors by senescent cells. This secretory activity contributes to chronic inflammation and tissue remodeling, exacerbating the autoimmune response and further beta-cell dysfunction in T1D.

In T1D, beta cells subjected to chronic stress and immune attack can enter a state of senescence. During senescence, beta cells stop proliferating and adopt the SASP, which involves the secretion of numerous pro-inflammatory molecules. This SASP can propagate local inflammation, attracting immune cells to the pancreas and worsening beta-cell destruction. The transcriptional regulation of SASP in beta cells has been linked to bromodomain extra-terminal (BET) proteins, such as Brd4, which interact with various proteins to activate SASP-related genes [130,131].

Targeting the SASP in beta cells offers several potential advantages. By reducing local inflammation in the pancreas, SASP modulation could slow the autoimmune destruction of beta cells. This strategy could help preserve residual beta-cell function, which is crucial for maintaining endogenous insulin production and better glycemic control. Clinical trials are exploring the efficacy of agents that target senescent cells or their secretory profiles in improving outcomes for T1D patients [130,132,133].

However, there are challenges and disadvantages to targeting the SASP. The complexity and heterogeneity of the SASP responses among different beta cells and individuals make it challenging to design universal therapies. The broad and diverse array of secreted factors means that completely inhibiting the SASP might impair beneficial immune responses. Additionally, the long-term effects of modulating SASP in beta cells are not fully understood, and there is a risk of unintended side effects if therapies inadvertently affect other cells in the body [130,132,134].

Recent studies have begun to unravel the mechanisms regulating SASP in beta cells. For instance, the NOD mouse model has been instrumental in studying beta-cell senescence and SASP. Research has shown that senescent beta cells in these models contribute to disease progression, and interventions targeting SASP components have shown promise in preclinical trials [130]. Understanding the transcriptional regulation of SASP in beta cells, including the roles of BET proteins like Brd4, is crucial for developing targeted therapies [130].

Continued exploration of SASP in beta cells aims to refine these therapeutic strategies. Ongoing clinical trials are assessing various senolytic and senomorphic agents to determine their efficacy and

safety in T1D patients. These studies are crucial for translating preclinical findings into viable treatments that could significantly improve the management of T1D. The Novel Immunotherapeutic Strategies in Type 1 Diabetes discussed above are summarized in Table 2, offering an overview of their mechanisms of action, key advantages, and associated challenges.

7. Conclusion

T1D remains a significant global health challenge due to its complex autoimmune nature and the lifelong requirement for exogenous insulin therapy. Despite advances in insulin delivery and glucose monitoring technologies, achieving optimal glycemic control and preventing long-term complications remain challenging for many patients. Therefore, the development of effective immunotherapeutic strategies to preserve or restore beta cell function is of paramount importance.

Antigen-independent therapies, such as antibody-based treatments and cytokine inhibitors, have shown promise in modulating the immune response and preserving beta cell function. Agents like Abatacept and Teplizumab have provided valuable insights into the potential of targeted immunomodulation, although challenges such as long-term efficacy and safety need further exploration. Similarly, cytokine inhibitors like Anakinra and Etanercept highlight the role of inflammatory pathways in T1D pathogenesis and present opportunities for therapeutic intervention.

Antigen-dependent strategies, including autoantigen vaccination, offer the potential for more specific modulation of the autoimmune response. While clinical trials of GAD65 and other autoantigen vaccines have yielded mixed results, they underscore the complexity of inducing immune tolerance in T1D. Refinements in vaccine formulations, dosing regimens, and combination therapies may enhance their therapeutic efficacy.

Beta cell therapies, particularly islet transplantation, have demonstrated the potential to achieve insulin independence in a subset of patients. However, the need for lifelong immunosuppression and limited donor availability remains significant barriers. Advances in encapsulation technologies and immunomodulatory protocols are critical to overcoming these challenges and making islet transplantation a more viable option for a broader patient population.

Stem cell therapies, including the use of mesenchymal stem cells (MSCs) and autologous hematopoietic stem cells (HSCs), represent a cutting-edge frontier in T1D treatment. These approaches not only aim to regenerate beta cells but also modulate the immune system to create a more tolerant environment. Ongoing research into optimizing stem cell sources, delivery methods, and combination with other therapies will be crucial for their clinical success.

Novel immunotherapeutic strategies, such as Chimeric Antigen Receptor (CAR)–Tregs therapy, offer innovative ways to enhance immune regulation and protect beta cells. Additionally, emerging approaches involving gut microbiota modulation and JAK-STAT pathway inhibition highlight the diverse mechanisms that contribute to T1D pathogenesis and present new avenues for intervention.

In summary, the landscape of T1D treatment is rapidly evolving, driven by advances in our understanding of disease mechanisms and the development of innovative therapeutic approaches. While significant challenges remain, the progress in immunotherapy, beta cell preservation, and regenerative medicine offers hope for more effective and durable treatments. Continued research, collaboration, and clinical translation of these strategies are essential to achieve the ultimate goal of curing T1D and improving the quality of life for those affected by this disease. Future efforts should prioritize personalized therapeutic approaches, combining multiple modalities to address the heterogeneous nature of T1D and maximize therapeutic benefits for patients.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Malek Zarei: Conceptualization, Resources, Writing – original draft, Writing – review & editing. **Mohammad Abbas Sheikholeslami:** Investigation, Writing – original draft. **Masoud Mozaffari:** Investigation, Writing – original draft, Writing – review & editing. **Yassar Mortada:** Methodology, Writing – original draft.

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