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Rethinking Type-1 Diabetes Treatment: Emerging Medicines Based on AAT Therapy and C-peptide Preservation Therapy

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Abstract

The increasing number of cases, especially in the younger age group, along with the lack of accessible clinical solutions, make Type-1 Diabetes (T1D) a growing global health concern. While gene therapy and transplantation approaches are promising avenues, their excessively high costs and logistical difficulties make them inaccessible to the majority and can impose a financial burden on those suffering from it, adding to the challenges already faced by these advanced techniques. Therefore, it becomes a necessity to develop novel pharmacotherapy that can be easily integrated into routine clinical practice and effectively curb β-cell damage while also being financially feasible. In the present study, the authors discuss various such economic and feasible options for treating Type 1 Diabetes, such as α-1 antitrypsin (AAT) therapy and C-peptide preservation therapy. AAT therapy involves the injection of the AAT agent along with insulin, which stimulates the tyrosine phosphorylation of insulin receptor (IR) and insulin receptor substrate-1 (IRS-1), typically stimulated by insulin in a non-diabetic individual. This therapy aims to enhance insulin sensitivity while reducing the autoimmune response targeting the β-cells. On the other hand, C-peptide preservation therapy uses drugs like anti-thymoglobulin (ATG) and teplizumab which are designed to prevent the depleting levels of C-peptide in T1D patients as it is related to the drop in insulin levels. This therapy, thus, mitigates the adverse effects associated with T1D, such as nerve damage and problems with blood vessels in the heart, eyes and kidneys. In the present manuscript, the authors aim to explore the efficiency of these newly emerged therapies in fighting against T1D.

Keywords: Type-1 diabetes, α-1 antitrypsin, C-peptide, teplizumab, novel treatments

INTRODUCTION

Type-1 diabetes (T1D) is a chronic condition in which the body's immune system mistakenly attacks and destroys insulin-producing β-cells in the pancreas, requiring lifelong insulin therapy [1]. The exact cause of T1D is not fully understood, but it is believed to involve a combination of genetic and environmental factors. WHO estimates that 422 million people worldwide suffer from diabetes, with T1D making up around 10% of all cases. This condition is often diagnosed in children, adolescents, and young adults, leading to substantial healthcare expenses for individuals and their families.

Managing T1D involves lifelong insulin therapy to regulate blood sugar levels, in addition to regularly monitoring blood sugar, following a balanced diet, and engaging in physical activity. Treatment options include injections and insulin pumps, with various types of insulin available based

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on individual needs and preferences [2]. In India, managing T1D typically involves similar principles of insulin therapy as well as lifestyle adjustments and considerations. However, the costs of insulin, glucose monitoring tools, and regular medical check-ups can be costly, resulting in significant financial stress and potential barriers to accessing proper healthcare, particularly in countries like India where access to affordable healthcare and medications is a major concern [3]. This financial strain also has far-reaching impacts on individuals and their families.

While the financial burden of T1D treatment is well-documented, research focusing on cost-effective therapeutic solutions remains limited. The present article addresses this gap by discussing α-1 antitrypsin (AAT) therapy using the AAT agent injected along with insulin and C-peptide preservation therapy using drugs like anti-thymoglobulin (ATG) and teplizumab therapy and discusses the financial challenges associated with T1D treatment and offers solutions to ease the burden on patients and families. It majorly emphasizes on new medications and strategies aimed at enhancing affordability and accessibility, empowering T1D patients with cost-effective options and thus exploring their potential to shift T1D management from lifelong insulin dependence towards more sustainable and affordable solutions. Additionally, it serves as a resource for healthcare providers and policymakers seeking to understand and address the financial barriers faced by T1D patients, ultimately fostering the growth of more affordable healthcare solutions.

METHODOLOGY

This review article systematically examines the literature concerning cost-effective therapeutics for Type 1 Diabetes (T1D). The methodology follows a structured approach to ensure comprehensive coverage of relevant studies and to uphold the integrity of the review process.

Literature Search

A thorough literature search was conducted using the following databases: PubMed, Liebertpub, PNAS, Sage Journals, and Journal of Social Health and Diabetes, Diabetologia and many others. These sources were chosen for their relevance to biomedical research and their robust collection of healthcare literature.

Search Terms

The selection of literature was guided by key terms integral to the research question. The terms used were “type-1 diabetes”, “α-1 antitrypsin”, “C-peptide”, “teplizumab”, “affordable medications” and “novel treatments”.

Time Frame and Language

The search was confined to studies published between the years 2010 and 2024, reflecting the most recent advancements in T1D treatments, and was limited to works published in English to ensure consistency and comprehensibility during analysis.

Selection Process

Our selection process began with an initial screening of titles and abstracts to exclude irrelevant publications. This was followed by a thorough full-text review of the shortlisted articles to assess their eligibility based on predetermined inclusion criteria – relevance to T1D cost-effective therapeutics and contribution to novel treatment advancements.

Inclusion Criteria

Studies included in this review were those that directly addressed T1D treatment and management strategies, provided insights into the cost-effectiveness of treatments, and discussed emerging therapies with the potential to transform current treatment protocols.

Data Extraction and Synthesis

Relevant data from the included studies were meticulously extracted, encompassing study design, population, intervention details, outcomes, and findings related to the cost and efficacy of T1D

therapies. The extracted data were then synthesized narratively to draw meaningful conclusions that could inform further research directions and clinical practices.

Quality Assessment

A critical appraisal of each study's methodology was conducted to assess the quality and bias of the evidence presented, thus ensuring that the conclusions drawn are based on rigorous and credible scientific evidence.

This review was conducted in accordance with rigorously established scientific review guidelines to ensure the validity and reliability of the findings. It serves as a foundation for the identification of effective, affordable, and innovative treatments that could revolutionize the current T1D therapeutic landscape.

CURRENT THERAPEUTICS AND THEIR CHALLENGES

T1D requires life-long management and relies heavily on the exogenous administration of insulin and vigilant blood glucose monitoring. Advances in insulin therapy include the development of a range of insulin analogues like rapid-acting, short-acting, intermediate-acting, long-acting, and ultra-long-acting insulins, which aim for more physiological blood glucose control. These insulins are delivered via multiple daily injections or continuous insulin pump infusions [1]. Recent technological interventions include the hybrid closed-loop system, providing automated insulin delivery by integrating continuous glucose monitoring with insulin pumps.

Despite these advances, there remain significant challenges. Insulin therapy requires precise dose adjustments and lifestyle coordination. Hypoglycemia and hyperglycemia are perpetual risks with tight glycemic control. Furthermore, the cost and accessibility of insulin analogues pose significant issues for many patients in India, where personal healthcare expenditures are high, and insurance coverage is limited [3].

Glucose sensors have greatly improved the quality of life for individuals with T1D by providing real-time glucose levels and trends. Nevertheless, these devices can sometimes be inaccurate, especially during rapid glucose fluctuations, and lag times in glucose reporting can complicate management. These sensors are also expensive and less accessible in low-resource settings, such as certain parts of India, hindering their widespread adoption.

Islet transplantation offers an alternative therapeutic approach with the potential for insulin production in patients with T1D [1]. This procedure involves harvesting islets from donor pancreases and transplanting them into a patient's liver, where they begin to produce insulin. Despite its promise, there are significant challenges, such as limited donor availability, islet viability post-transplant, and the need for long-term immunosuppressive therapy to prevent rejection [4].

On top of that, problems in the Indian healthcare picture include high treatment costs, restricted access to modern therapies, and a need for healthcare infrastructure improvements. Insulin and related supplies can be prohibitively expensive, and islet transplantation, which is still in the experimental stages in India, incurs enormous costs not just for the treatment but also for the lifelong immunosuppression required [4]. Additional research and investment must be done to make these treatments more affordable and widely accessible.

NEED FOR NOVEL PHARMACOTHERAPY

The cost of diabetes care in India varies broadly depending on urban or rural settings, access to healthcare, and the type of treatment required. On average, the annual expenditure by patients on diabetes care was reported to be around Rs. 10,000 in urban areas and Rs. 6,260 in rural areas [5]. The median annual family income of T1D patients ranges widely from Rs. 10,000 to 600,000, making the

cost a significant burden for many families, especially given that insulin therapy and blood glucose monitoring are lifelong necessities [6].

Scientists are looking for novel pharmacotherapies for T1D which have several advantages over traditional treatments, including improved glycemic control, a lower risk of complications, and a more favorable side effect profile. Furthermore, they should offer increased convenience through simplified treatment regimens, and they also should show promise in modifying the underlying disease process, conserving residual insulin secretion, and potentially attaining a disease-free state with targeted therapies based on specific patient features [7]. Notably, these pharmacotherapies should be cost-effective, offering a long-term solution for both patients and healthcare systems.

The benefits of emerging pharmacotherapies for T1D should address the limitations of traditional therapy and use creative techniques, making them enticing options for patients and healthcare professionals looking for more effective, acceptable, and individualized treatment plans.

The following section describes novel therapies for T1D, with particular emphasis on teplizumab, a monoclonal antibody, and AAT therapy. The underlying autoimmune response of T1D is the target of both these therapies. We aim to assess their therapeutic potential and related issues while considering their implications for the future of diabetic care.

AAT Treatment

Introduction

AAT is a glycoprotein, specifically a serine protease inhibitor, primarily made in the liver that helps protect tissues from enzymes of inflammatory cells, especially elastase. It is also referred to as an α-1 proteinase inhibitor (α1-PI).

AAT weighs in at approximately 52 kDa. It is composed of a single polypeptide chain, which folds into a complex tertiary structure essential for its function. The synthesis of AAT is governed by the SERPINA1 gene located on chromosome 14, reflecting its significant genetic regulation. This protease inhibitor, with a reactive center loop that cleverly mimics the structure of typical substrates for these enzymes, allows it to effectively inhibit target proteases, protecting tissues from damage during inflammation [8].

From a pharmaceutical perspective, AAT has substantial therapeutic value, exhibiting potent anti-inflammatory, immunomodulatory, and tissue protective properties (Figure 1) [9]. AAT therapy has also demonstrated the potential to modulate the immune response and even contribute to the regeneration of β-cells in the context of T1D [10]. In clinical settings, AAT is typically administered through intravenous infusions, with the protein purified from the plasma of donors.

Mechanism of Action

The mode of action of AAT includes dampening the autoimmune response by influencing immune cells, like T cells and macrophages, which are responsible for the attack on insulin-producing β-cells in the pancreas [11]. This regulation helps in preserving the function and viability of β-cells. Additionally, AAT provides a protective effect by inhibiting harmful enzymes and reducing pro-inflammatory cytokines, thereby minimizing β-cell damage [11]. Its role in enhancing pancreatic tissue repair helps create a conducive environment for the healing and regeneration of affected cells.

Effect on T1D

AAT appears to have multiple effects in combating T1D (Figure 2), particularly through modulating the immune response, based on experiments conducted on non-obese diabetic mice, which serve as a model for this autoimmune disease, by Koulmanda et al. (2008).

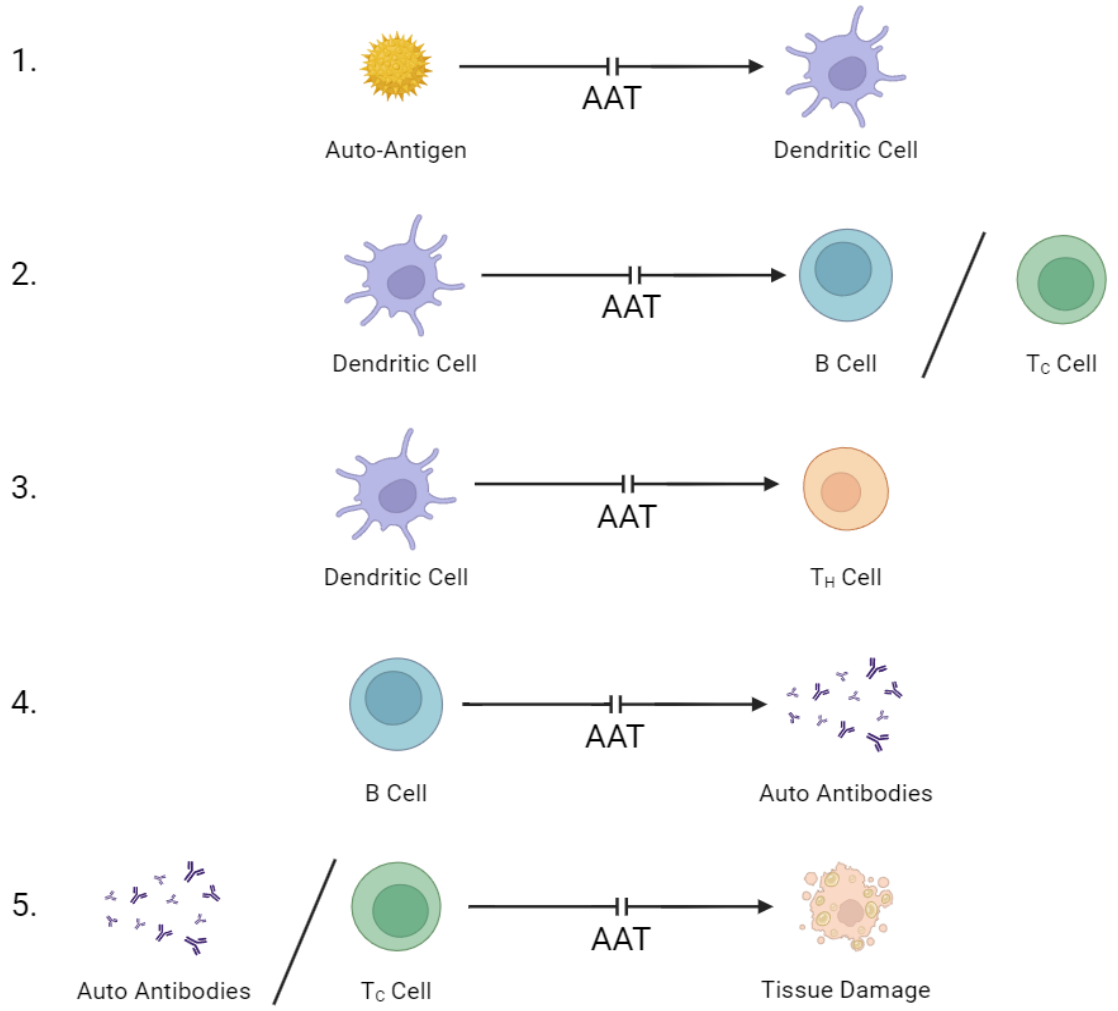

Figure 1. Pharmaceutical functions of AAT.
1. AAT inhibits dendritic cell activation and functions. 2. It interacts with different cell types and blocks their inflammatory signals. 3. By altering the inflammatory gene expression, AAT can reduce the inflammatory response. 4. AAT reduces auto-antibody production from B cells. 5. By inhibiting proteinases, it protects them from tissue damage.

The experiments report that AAT treatment:

- *Modulates immune tolerance:* AAT treatment in NOD mice with new-onset T1D appears to tilt the immune system towards tolerance of pancreatic β-cells. It prevents the autoimmune destruction of syngeneic islet grafts, inducing a state of specific immune tolerance to the islet β-cells, thereby allowing the mice to maintain normoglycemia even after their remnant β-cells were chemically destroyed and then replaced with syngeneic islets [8].
- *Alters the balance of immunity and inflammation:* AAT treatment leads to a shift in proinflammatory to anti-inflammatory cytokine expression. It also results in an increased expression of regulatory T cell genes over T cell Th1/Th17 effector genes, indicating a stronger anti-inflammatory immune profile [8].
- *Improves insulin sensitivity and signaling:* The treated NOD mice demonstrate normalized response to insulin, suggesting that AAT treatment can erode insulin resistance in these mice. This normalization of insulin signaling is critical as it allows for the better disposal of blood glucose [8].
- *Restores β-cell function:* AAT treatment has been reported to foster an environment favorable to the survival and possibly regeneration of β-cells. In studies, treated NOD mice have shown

improvement in β-cell health, with a decrease in lymphocytic infiltration within the islets, which is often a hallmark of autoimmune attack in T1D. By minimising immune cell aggression towards β-cells, AAT may help in preserving and restoring the functional mass of these cells [8].

- *Modulates insulin receptor signaling:* Efficient insulin signaling is crucial for glucose uptake and use; thus, AAT might help restore normal metabolic processes by improving the insulin signaling pathway, including downstream signals such as IRS-1, which is key in mediating the action of insulin [8].

The combined effects of these processes can contribute to the prevention of the onset of T1D, the reversal of hyperglycemia, and the avoidance of fatal complications such as anaphylaxis, as seen in the animal models [8].

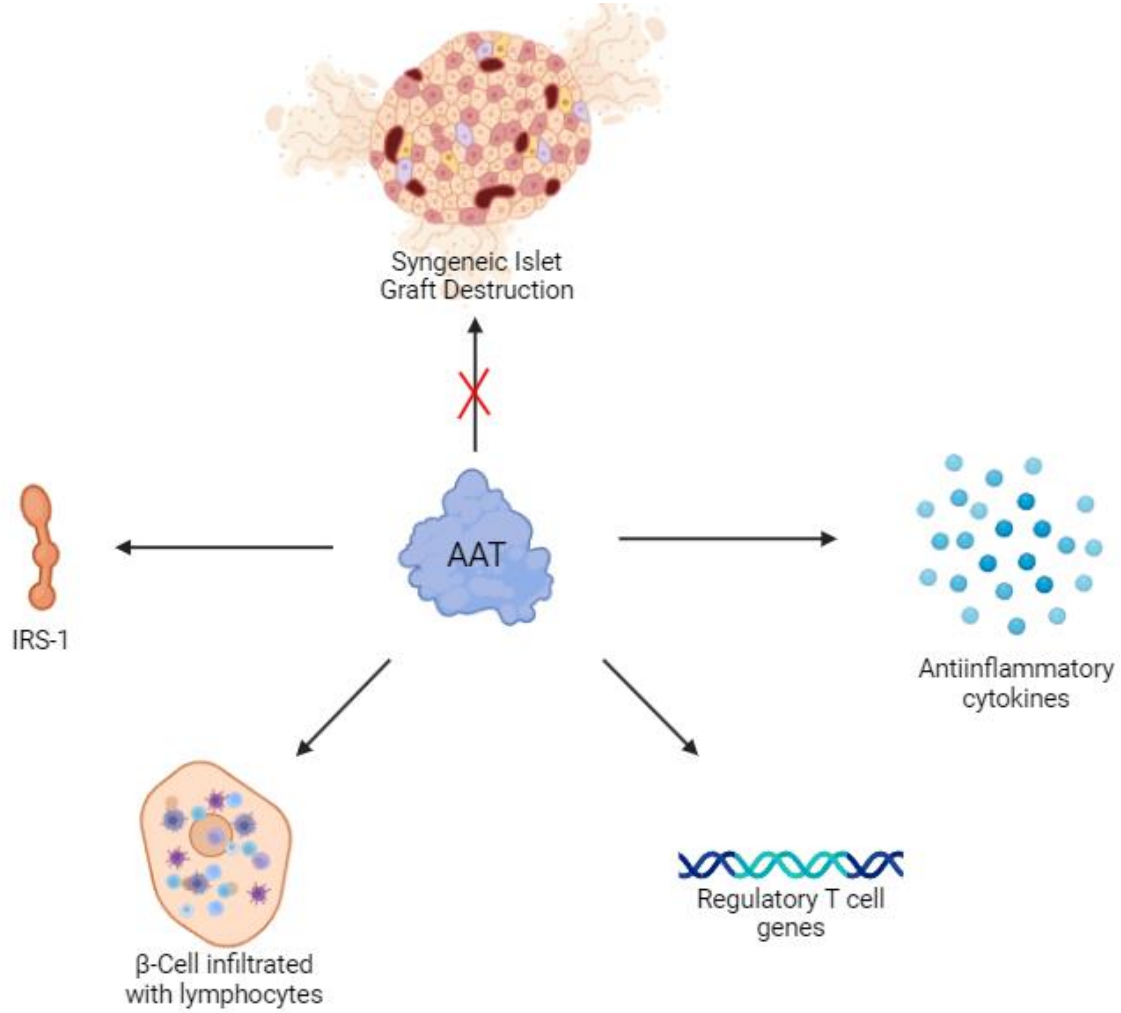

Figure 2. Multiple effects of AAT.
1. AAT inhibits dendritic cell activation and functions. 2. It interacts with different cell types and blocks their inflammatory signals. 3. By altering the inflammatory gene expression, AAT can reduce the inflammatory response. 4. AAT reduces auto-antibody production from B cells. 5. By inhibiting proteinases, it protects them from tissue damage.

Advantages and Drawbacks

Advantages of AAT as a treatment for T1D include its ability to impart multiple protective effects. It fosters immune tolerance to β-cells, reducing autoimmune destruction, and potentially regenerating these cells. Studies on NOD mice have indicated that AAT can prevent β-cell damage, promote

regeneration, and exert anti-inflammatory effects that improve insulin sensitivity. By modulating immune responses to be more tolerant and reducing pancreatic inflammation, AAT could be a more comprehensive treatment than current therapies centered on only managing glucose levels or suppressing immunity [8, 10].

However, there are limitations to this therapy as well. Considerable research is still required to understand the complete mechanisms of action of AAT and to optimize its therapeutic efficacy [11]. In terms of practical application, there could be challenges in translating findings from NOD mouse models to human T1D because of differences between species and immune system function. Additionally, the initial hyperglycemic phase seen in the AAT-treated NOD mice raises concerns about the timing and monitoring of treatment efficacy, meaning patients may still need to manage hyperglycemia with conventional insulin therapy for several weeks after AAT treatment begins [8]. Lastly, clinical trials are necessary to determine not only the efficacy and safety of AAT in human subjects with T1D but also its economic viability as a standard treatment option [11].

Teplizumab Treatment

Teplizumab as a Therapeutic Agent

Teplizumab is an immunoglobulin structured as a typical Y-shaped antibody composed of two identical heavy chains and two identical light chains linked by disulfide bonds. This structure is integral to its mechanism of action, which involves distinct antigen-binding sites that are highly specific to the CD3ε heterodimer found on the surface of T-cells. By binding to the CD3ε receptors, teplizumab impacts T-cell signaling and reduces the number and function of effector T-cells, simultaneously promoting regulatory T-cell activities [12].

Clinical trials have shown teplizumab's capability to preserve endogenous C-peptide levels, a proxy for β-cell function, indicating that it can maintain some insulin production in individuals with recent-onset T1D. This preservation of C-peptide was observed for up to two years in newly diagnosed T1D subjects, which suggests an induction of immune tolerance – a beneficial therapeutic outcome in managing T1D [12].

Teplizumab is administered intravenously. The therapy course consists of a single two-week treatment cycle intended to provide long-term immunomodulatory effects. The administration regimen emphasises the necessity of administering teplizumab in a way that enhances its ability to establish immunological tolerance while minimising side effects and treatment burdens. The pharmaceutical formulation, like any medicine, is tailored to ensure the antibody's stability, bioavailability, and potency.

Mechanism of Action

Teplizumab aims to alleviate the autoimmune attack against pancreatic β-cells. The antibody's engagement with CD3ε receptor disrupts normal T-cell signal transduction, leading to altered cellular responses ranging from partial activation to anergy, which is crucial for its therapeutic action (Figure 3) [13]. This strategic binding to CD3ε on T cells attenuates the effector T-cell responses, which are the main contributors to the autoimmune destruction of insulin-producing β-cells. As the activity of these effector T cells diminishes, the inflammatory cascade within pancreatic tissue subsides. Teplizumab also improves the function of regulatory T cells, which enhances immunological tolerance. Regulatory T cells act as the immune system's peacekeepers, limiting excessive reactions and avoiding collateral damage to healthy cells [14]. Teplizumab suppresses autoreactive immune cells and protects pancreatic cells by boosting these regulatory cells [15].

As these processes converge, teplizumab develops immunological tolerance, successfully lowering autoimmune aggressiveness against insulin-producing β-cells. The preservation of β-cell function, as indicated by persistent C-peptide levels, emphasises the need for immunological regulation. This

biomarker of β-cell activity implies that, particularly in new-onset T1D, there is a key window during which teplizumab therapy can extend the temporary phase post-diagnosis when the pancreas produces significant insulin [16]. This outstanding longevity of action suggests a potential "reset" within immune system dynamics, resulting in a lingering balance between the immune system's aggressive effector activities and regulating systems [16]. This balance indicates a more permanent state of immunological homeostasis, which could prevent β-cell death for an extended duration.

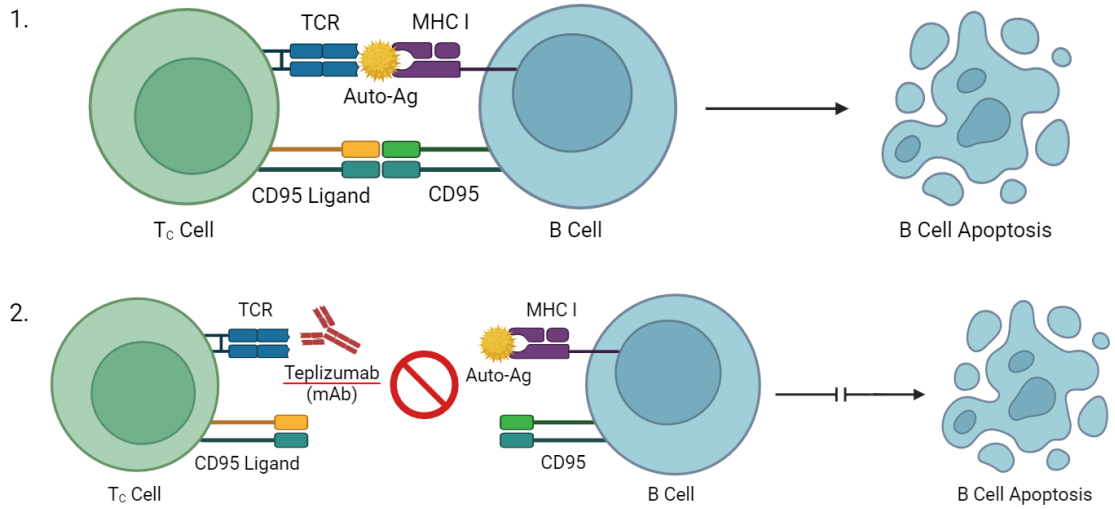

Figure 3. Mechanism of action of teplizumab.
1. The binding of CD95 with CD95 ligand induces the apoptosis of the pancreatic β cell. 2. The targeted binding of teplizumab to TCR reduces the effector T cell responses, which are the principal contributors to the autoimmune death of insulin producing β cells.

Effect on T1D

The key effects and mechanisms through which teplizumab suppresses the progression of T1D are listed below.

- *C-peptide preservation:* Teplizumab's efficacy in C-peptide preservation was ranked highly in clinical trials. Studies have demonstrated that this immunotherapy results in a slower decline of C-peptide levels compared with placebo, indicating preserved β-cell function and endogenous insulin production in individuals with recent-onset T1D [16].
- *Inducing immune tolerance:* Clinical studies have provided evidence of teplizumab inducing immune tolerance, manifested by a decrease in the quantity of effector T cells and an increase in the function of regulatory T cells. Additionally, teplizumab has been associated with an increase in anergic. T cells towards β-cell antigens, contributing to the prevention of further autoimmune damage [17].
- *Delaying onset in high-risk individuals:* By preserving β-cell function for a longer time and reducing the immune response of T cells against them leads to a precautionary effect thus extending the period of normal glucose tolerance hence potentially delaying the clinical onset of diabetes [16].
- *Selective immune modulation:* Teplizumab specifically targets CD3ε on T cells, which directly impacts autoreactive T cells responsible for β-cell destruction. The implications of such targeted therapy were discussed in the context of CD3ε's unique role in T-cell biology and the therapeutic advantage of modifying T-cell responses without inducing general immunosuppression [18].

Advantages and Drawbacks

With benefits obtained from this treatment which includes β-cell preservation demonstrated by maintained C-peptide levels indicating continued natural insulin secretion, teplizumab appears to be a promising treatment for type 1 diabetes. Notably, it may postpone the clinical development of T1D in individuals at high risk, hence reducing the need for additional insulin and averting future health complications. With an adequate safety profile that supports its use for long-term treatment, the drug's immune-specific activity provides selective immune system modulation, focusing on specific T cells that may reduce excessive immunosuppression and maintain infection defense capabilities [17].

Challenges include the need for routine monitoring to detect side effects including infections, the erratic nature of patient response, and the lack of certainty surrounding long-term safety and efficacy. Its intravenous administration is another potential drawback. Because of its anticipated greater cost, accessibility and cost-effectiveness are the concerns. But, as individuals might show lower insulin requirements and fewer problems, improving quality of life and potentially offsetting the initial cost may add to its cost-benefit ratio in long-term T1D management.

FUTURE THERAPEUTICS AND PERSPECTIVES

In the realm of T1D treatment, the future shines with the prospect of transformative therapies that aim not just to manage the condition, but to provide long-term solutions and ease the daily burden on patients. Understanding the immunopathology of the disease and identifying reliable biomarkers are essential to approach novel therapeutics. Pieces of research continue non-injectable insulin delivery, insulin replacement, beta cell transplants, regenerating beta cells, immunomodulatory drugs, and developing an artificial pancreas system.

Artificial pancreas systems aim for an entirely automated management system that can adjust to an individual's dynamic needs, minimizing the risk of both high and low blood sugar episodes [19]. Ongoing refinements in these technologies hold promise for improving patient outcomes and simplifying the complexities of daily diabetes care. By intervening early in the disease process, immunomodulation therapies aim to preserve pancreatic β-cell function, offering a window of opportunity to alter the course of T1D. This form of treatment could reduce long-term dependency on insulin and mitigate complications associated with T1D.

Gene therapies are also being explored with the long-term vision of addressing the genetic foundations of T1D. The therapeutic approach aims to reprogram the body's own cells to defend against autoimmune attacks or to resume insulin production [1]. Such cutting-edge treatments could one day offer a permanent cure for T1D, freeing patients from the constant monitoring and insulin therapy that currently defines diabetes management. β-Cell regeneration approach promises not just to replace the need for exogenous insulin but to restore the body's innate ability to regulate blood glucose levels. Together, these emerging therapies provide a hopeful view for individuals afflicted with T1D, signaling a shift from lifelong management to genuine, sustainable solutions that could redefine living with diabetes.

LIMITATIONS OF THE CURRENT LITERATURE REVIEW

This review article has several limitations worth noting. First, the literature search was confined to articles published between 2010 and 2024 and only in English, which may have excluded relevant studies conducted in other languages or before 2015 that could contribute additional insights into cost-effective T1D therapies.

Secondly, our methodology, while systematic, may possess inherent biases, including publication bias, where positive outcomes are more likely to be published than negative findings. This could skew the perceived effectiveness or cost-efficiency of the therapies discussed. Additionally, the review heavily focuses on novel and emerging treatments, such as AAT therapy and teplizumab, which, while

promising, may still be in the early stages of research. The long-term effectiveness, safety profiles, and real-world accessibility of these therapies have yet to be fully understood.

The article also notes that when this review is published, there's a chance that technology and medicine will develop quickly. As a result, the findings and suggestions may not represent the most recent research or newly created therapies after 2024. Finally, the financial analyses of T1D treatments discussed might not fully capture the indirect costs and socioeconomic impact on patients and families, which can vary widely based on geographic and individual circumstances.

These limitations highlight the need for ongoing research, the inclusion of broader and more diverse data sources, as well as the adoption of methodologies that account for a rapidly evolving healthcare landscape.

CONCLUSION

In conclusion, this review has explored the various obstacles that patients and their families experience when managing type 1 diabetes, with a focus on financial issues. Affordable treatments like teplizumab and AAT therapy, which can change the course of treatment by lowering the need for constant insulin therapy and slowing the advancement of the illness have been investigated.

Despite the promise of these emerging therapies, our findings must be interpreted considering the limitations inherent in the scope of literature reviewed, the language restrictions, potential publication biases, and the preliminary nature of novel treatment efficacies. Furthermore, the financial analyses may not capture the full spectrum of economic impact on patients.

The essential need for large-scale, long-term research to determine the long-term results, safety, and cost-effectiveness of these treatments is highlighted by our review. For these advancements to benefit the larger T1D community, intelligent healthcare policies and creative solutions are still needed, with accessibility and affordability remaining the two most important considerations. For this purpose, it is critical that research, clinical practice, and health policy all advance simultaneously.

By providing a thorough synthesis of the current state of T1D treatment and its economic considerations, a cooperative effort between scientists, healthcare providers, and policymakers to create an environment where the cost of T1D does not prevent access to novel therapies that enhance patient outcomes and quality of life has been suggested.

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