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RESEARCH ARTICLE

Efficacy of immunosuppression in preserving beta cell function and reducing insulin requirements in Type 1 diabetes mellitus: a comprehensive review

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Objectives: To evaluate the efficacy of immunosuppressive therapies in preserving pancreatic beta-cell function and reducing insulin requirements in patients with Type 1 diabetes mellitus (T1DM).
Design: A systematic review of 48 clinical trials conducted between 1986 and 2023, analysing the short- and long-term effects of various immunosuppressive treatments on beta-cell preservation.
Setting: Data were sourced from international databases including PubMed, Web of Science, Medline, and Cochrane Library.
Subjects: A total of 4 977 participants, of whom 3 084 were in immunosuppressive treatment groups and 1 893 in control groups. All subjects were diagnosed with T1DM.
Outcome measures: The primary outcome was the preservation of beta-cell function, as indicated by C-peptide levels. Secondary outcomes included changes in insulin requirements, glycaemic control (HbA1c), and safety profiles of the therapies.
Results: Short-term benefits in beta-cell preservation were observed with immunosuppressive agents such as cyclosporin and anti-CD3 monoclonal antibodies. However, these therapies did not consistently show long-term efficacy, with variability in patient responses. Adverse effects, such as nephrotoxicity and immune-related complications, were noted.
Conclusions: Immunosuppressive therapies offer potential benefits in reducing insulin dependency and preserving beta-cell function in T1DM. However, long-term efficacy and safety remain uncertain, necessitating further research into personalised treatment approaches to optimise outcomes.

Keywords: autoimmune, beta-cell preservation, immunosuppression, insulin dependency, Type 1 diabetes mellitus

Introduction

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disorder that results in the destruction of insulin-producing beta cells in the pancreas, leading to absolute insulin deficiency. This condition necessitates lifelong exogenous insulin therapy to manage blood glucose levels and prevent both acute and chronic complications such as diabetic ketoacidosis, cardiovascular disease, nephropathy, neuropathy, and retinopathy. T1DM typically manifests during childhood or adolescence but can occur at any age, posing a significant public health burden with a rising global incidence.[1,2]

Standard management of T1DM focuses on exogenous insulin replacement to maintain glycaemic control. However, this approach does not replicate the physiological insulin secretion patterns of healthy pancreatic beta cells, leading to suboptimal glycaemic control and an increased risk of both acute and chronic complications.[3] Consequently, there is considerable interest in developing therapeutic strategies that preserve residual beta-cell function to enhance metabolic control and reduce the long-term burden of the disease.[4]

The pathophysiology of T1DM is characterised by an autoimmune response in which autoreactive T cells target and destroy beta cells within the pancreatic islets. This autoimmune process is driven by complex interactions between genetic predisposition, environmental triggers, and immune dysregulation.[1,5] The loss of beta cells leads to a progressive decline in endogenous insulin production, resulting in hyperglycaemia and the onset of diabetes. Preserving residual beta-cell function during the early stages of T1DM could improve glycaemic control, reduce insulin requirements, and delay the onset of diabetes-related complications.[6]

Immunosuppressive therapies have emerged as a promising approach to modulating the autoimmune process in T1DM. These therapies aim to preserve residual beta-cell function by targeting the immune mechanisms responsible for beta-cell destruction.[7] Various immunosuppressive agents, including cyclosporin, azathioprine, mycophenolate mofetil, and biologics such as anti-CD3 monoclonal antibodies, have been evaluated in clinical trials for their potential to alter the course of T1DM.[8,9]

Despite the promise of immunosuppressive therapies, challenges remain in their application for T1DM. Long-term efficacy, safety, and patient variability in response to treatment are significant concerns.[7,10,11] Additionally, while some therapies have shown short-term benefits in preserving beta-cell function, none have achieved long-term remission or reversal of T1DM.[12] This systematic review aims to evaluate the current literature on the efficacy of immunosuppressive therapies in T1DM, with a focus on preserving beta-cell function and reducing insulin dependency. The review synthesises data from 48 clinical trials to provide a comprehensive assessment of the potential and limitations of these therapies in managing T1DM.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13] The review focused on evaluating the effectiveness of immunosuppressive therapies in preserving pancreatic beta cell function and reducing insulin requirements in individuals diagnosed with T1DM.

Search strategy

A comprehensive literature search was conducted across four major databases: PubMed, Web of Science, Medline, and the Cochrane Library. The search strategy involved using keywords such as "Type 1 Diabetes Mellitus", "Immunosuppression", "Beta Cell Function", "C-peptide", and "Insulin Requirement". The search was not limited by publication date to capture a broad spectrum of studies. In addition to database searches, reference lists of relevant articles were manually reviewed to identify any additional studies that met the inclusion criteria.

Inclusion criteria for this review were as follows: (1) studies involving individuals diagnosed with T1DM; (2) studies where participants received immunosuppressive therapy aimed at preserving beta-cell function; (3) randomised controlled trials (RCTs), clinical trials, and observational studies; (4) studies reporting outcomes related to beta-cell function (measured by C-peptide levels) and insulin requirements. Exclusion criteria included studies focusing on islet cell transplantation, animal or in vitro studies, and studies not published in English. Studies that did not report relevant clinical outcomes or those that were case reports or review articles were also excluded.

Study selection

The initial search yielded 820 studies. After removing duplicates and applying the inclusion and exclusion criteria, 348 studies remained. Titles and abstracts were screened, leading to the exclusion of 252 studies that did not meet the inclusion criteria. Full-text articles were then reviewed, resulting in the final inclusion of 48 clinical trials that were relevant to the research question.[4,11,12,14–58] These trials were selected based on their quality, relevance, and the comprehensiveness of the data presented (Figure 1).

Data extraction and synthesis

Data extraction was conducted independently by two reviewers using a standardised form to ensure consistency and accuracy. Extracted data included study design, sample size, duration of therapy, type of immunosuppressive agent used, primary and secondary outcomes, and reported adverse events. The primary outcome of interest was the preservation of beta-cell function, measured by C-peptide levels, which serve as a surrogate marker for endogenous insulin production. Secondary outcomes included changes in insulin requirements, glycaemic control (HbA1c levels), incidence of hypoglycaemic events, and safety profiles of the therapies.

The extracted data were synthesised into a narrative summary, given the heterogeneity of the included studies in terms of study design, patient populations, and interventions. The risk of bias in the included studies was assessed using the Cochrane Risk of Bias tool, which evaluates potential sources of bias across several domains, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting (see Appendix 1).[59]

Results

The final analysis included 48 clinical trials published between 1986 and 2023, covering a period of 37 years. These studies involved a total of 4 977 patients, with 3 084 in the experimental groups and 1 893 in the control groups (placebo or standard of care). The majority of studies were randomised controlled trials (RCTs), with 35 out of 48 trials being double-blind. The remaining 13 trials were open-label or case-controlled studies. The studies evaluated a range of immunosuppressive agents (summarised in Appendix 2 and 3), including cyclosporin, anti-CD3 monoclonal antibodies, azathioprine, mycophenolate mofetil, rituximab, and other biologics.

Cyclosporin

Cyclosporin was one of the first immunosuppressive agents evaluated for its potential to preserve beta-cell function in T1DM. A landmark multicentre double-blind trial conducted by Feutren et al. demonstrated that cyclosporin significantly increased the rate and duration of remissions in newly diagnosed T1DM patients. At nine months, 24.1% of patients in the cyclosporin group were in complete remission compared with 5.8% in the placebo group ($p < 0.01$). This early success suggested that cyclosporin could slow the autoimmune destruction of beta cells, thereby preserving their function during the early stages of T1DM.[14]

Subsequent studies, including those by the Canadian-European Randomised Control Trial Group and Assan et al. confirmed the initial findings but also highlighted significant limitations.[15,16] While cyclosporin was effective in inducing remission, the benefits were not sustained after discontinuation of therapy. Patients who initially experienced remission often relapsed into insulin dependency once cyclosporin was withdrawn, indicating that the drug did not fundamentally alter the underlying autoimmune process.[16] Furthermore, long-term use of cyclosporin was associated with nephrotoxicity, hypertension, and an increased risk of infections, which limited its utility as a chronic therapy for T1DM.[60,61]

Anti-CD3 monoclonal antibodies

Anti-CD3 monoclonal antibodies, including teplizumab and otelixizumab, have shown promise in preserving beta-cell function in newly diagnosed T1DM patients. Herold et al. conducted a randomised controlled trial with teplizumab, demonstrating improved C-peptide responses and reduced insulin requirements for up to two years post-treatment without continued immunosuppression. This finding suggested that anti-CD3 therapy could induce a more durable remission compared with earlier immunosuppressive agents like cyclosporin.[17]

The efficacy of teplizumab was further supported by a study conducted by Sherry et al.[12] Sherry et al. reported that patients treated with teplizumab showed a slower decline in C-peptide levels compared with placebo, indicating that the therapy could extend the period of endogenous insulin production. However, the studies also noted that higher doses of teplizumab were associated with increased adverse events, including cytokine release syndrome and leukopenia, raising concerns about the safety of long-term use of anti-CD3 monoclonal antibodies.[12,17]

The potential of otelixizumab, another anti-CD3 monoclonal antibody, was evaluated in the DEFEND-1 trial, which showed that a single course of therapy preserved beta-cell function

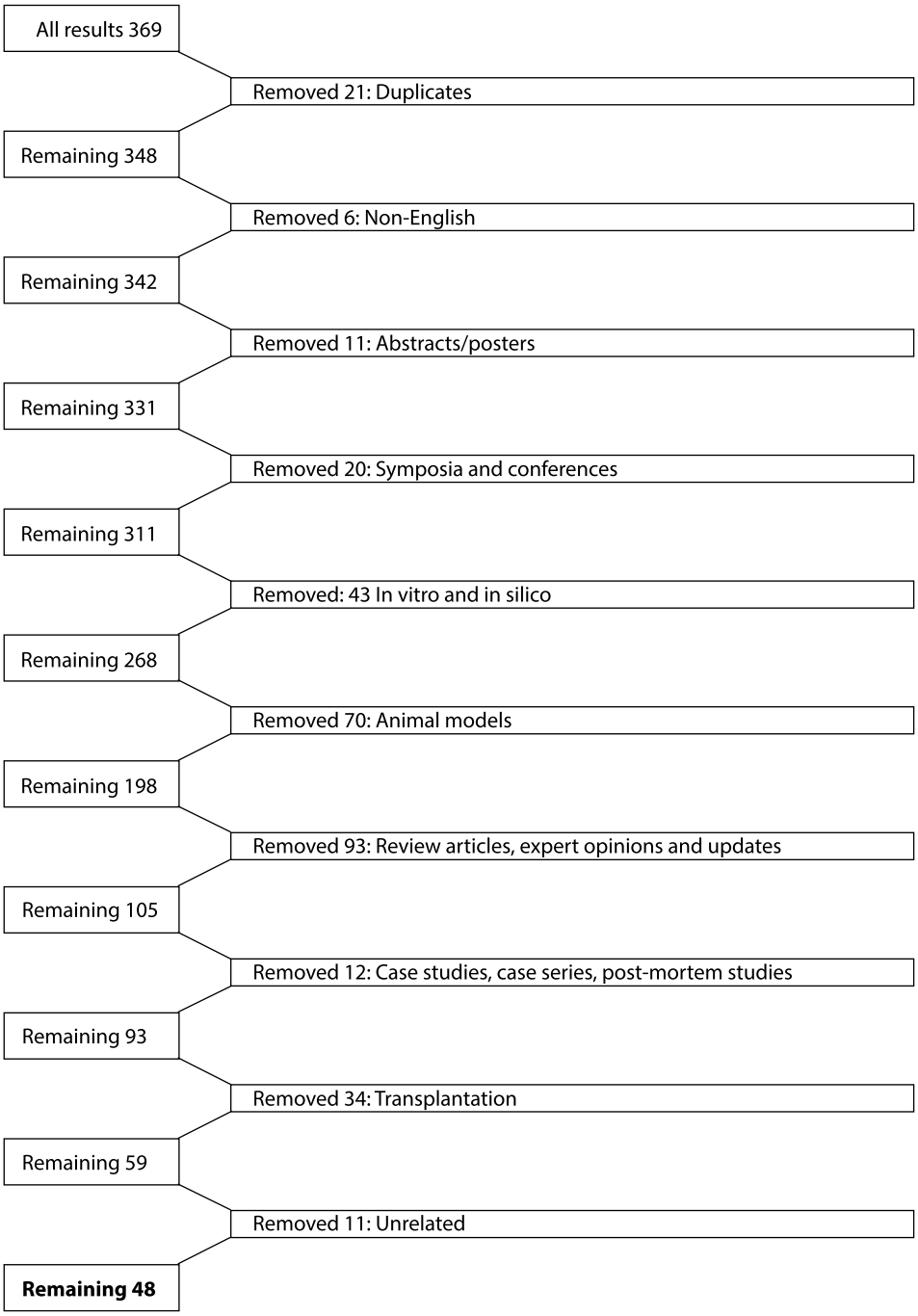

Figure 1: Search results charted.

for at least 18 months in newly diagnosed T1DM patients.[62] However, like teplizumab, otelixizumab was associated with significant immune-related adverse events, including transient Epstein–Barr virus reactivation and lymphopenia, which limited its broader application.[8]

Combination therapies

Combination therapies involving multiple immunosuppressive agents have been explored to enhance beta-cell preservation and reduce insulin requirements. The rationale behind combination therapies is to target multiple aspects of the autoimmune response simultaneously, potentially improving therapeutic outcomes.[18] Moncada et al. investigated the combination of azathioprine and thymostimulin in newly diagnosed T1DM patients and reported improved long-term remission rates compared with monotherapy. The study found that patients receiving the combination therapy had higher C-peptide levels and required lower insulin doses, suggesting a potential synergistic effect.[19]

Haller et al. evaluated the combination of antithymocyte globulin (ATG) and granulocyte colony-stimulating factor (GCSF), finding that it preserved beta-cell function and reduced HbA1c levels in new-onset T1DM patients. This study was particularly noteworthy because it included a longer follow-up period of two years, allowing for a more comprehensive assessment of the long-term efficacy and safety of the combination therapy.[4] However, the efficacy of combination therapies varied across studies, with some trials reporting limited benefits or increased adverse events, highlighting the need for further research to identify the most effective combinations and dosing regimens.[9]

Other notable studies include the combination of mycophenolate mofetil and daclizumab, which was evaluated in the ABATE trial. The study demonstrated that the combination therapy preserved beta-cell function better than placebo, but the benefits were modest and accompanied by significant side effects, such as gastrointestinal disturbances and increased infection rates.[18] These findings suggest that while combination therapies hold promise, their application in T1DM requires careful consideration of the risk–benefit profile.

Rituximab and B-cell depletion therapies

Rituximab, a monoclonal antibody targeting CD20 on B cells, has been investigated for its potential to modulate the autoimmune process in T1DM. Pescovitz et al. conducted a randomised controlled trial in newly diagnosed T1DM patients and found that rituximab treatment resulted in a slower decline in C-peptide levels compared with placebo. The study provided evidence that B-cell depletion could be a viable strategy for preserving beta-cell function in the early stages of T1DM.[7]

The TrialNet Study Group further explored the role of rituximab in combination with abatacept, a T-cell co-stimulation blocker, to assess whether dual immunomodulation could enhance beta-cell preservation. The combination therapy showed a more pronounced effect on C-peptide preservation compared with monotherapy with rituximab or abatacept alone, suggesting a potential additive effect of targeting both B cells and T cells.[20] However, the increased risk of infections and infusion reactions associated with rituximab therapy raised concerns about its long-term safety, particularly in paediatric populations.[7]

Novel immunotherapies and cytokine modulation

Novel immunotherapies targeting specific immune pathways represent an exciting avenue for T1DM treatment. These therapies aim to modulate the immune response in a more targeted manner, potentially reducing the autoimmune destruction of beta cells while minimising the broader immunosuppressive effects seen with traditional therapies.[10] Raz et al. studied DiaPep277, a heat-shock protein peptide, and found that it preserved endogenous insulin production by shifting the cytokine profile towards a Th2 phenotype. However, despite initial promising results, subsequent studies on DiaPep277 were less conclusive, and the therapy did not advance to widespread clinical use.[21]

Additionally, studies on cytokine modulation, such as the use of interleukin antagonists, have shown mixed results. Greenbaum et al. reported that IL-6 receptor blockade did not significantly slow beta-cell loss, suggesting that targeting this specific cytokine may not be sufficient to alter the course of T1DM.[22] In contrast, von Herrath et al.[23] found that a combination of anti-IL-21 antibody and liraglutide reduced the decline in C-peptide levels, indicating potential for beta-cell preservation.[23]

The success of these novel immunotherapies highlights the importance of understanding the immune mechanisms involved in T1DM. However, the variability in patient responses and the lack of consistent long-term benefits underscore the challenges of developing effective immunotherapies for T1DM. The immune system's complexity and the multifactorial nature of T1DM suggest that a single-target approach may be insufficient to achieve long-term remission. Instead, combination therapies that address multiple aspects of the immune response may be necessary to improve outcomes.[21,22]

Discussion

The results of this systematic review highlight the complex and multifaceted nature of immunosuppressive therapy in T1DM. While some therapies, such as cyclosporin and anti-CD3 monoclonal antibodies, have shown promise in preserving beta-cell function and reducing insulin requirements, their long-term efficacy remains uncertain. The variability in patient responses across the studies suggests that individual genetic and immunological profiles play a significant role in determining the success of these therapies.[8]

Cyclosporin and remission rates

Cyclosporin was one of the first immunosuppressive agents to be studied in T1DM, and early results were promising, particularly in increasing remission rates. The multicentre trial by Feutren et al. demonstrated that cyclosporin could significantly increase the rate and duration of remissions in newly diagnosed patients, suggesting that early intervention with immunosuppressive therapy could alter the disease course.[14] However, the lack of sustained benefits after discontinuation of cyclosporin indicates that while the drug may provide short-term improvements, it does not fundamentally alter the underlying autoimmune process driving beta-cell destruction.[14,16]

The relapses observed in patients after cyclosporin was withdrawn highlight a critical challenge in the long-term management of T1DM with immunosuppressive therapy. The need for continuous administration of cyclosporin to maintain its effects raises concerns about the potential for cumulative toxicity, particularly nephrotoxicity, which is a well-documented side effect of long-term cyclosporin use. Moreover, the immunosuppressive effects of cyclosporin may increase the risk of opportunistic infections, which could further complicate the management of T1DM.[61]

Anti-CD3 monoclonal antibodies

Anti-CD3 monoclonal antibodies, particularly teplizumab, have shown more durable benefits compared with cyclosporin. The ability of teplizumab to preserve C-peptide levels for up to two years post-treatment suggests that it may have a more profound impact on the autoimmune processes in T1DM. This could be attributed to the mechanism of action of anti-CD3 antibodies, which specifically target T cells involved in the autoimmune destruction of beta cells. By modulating T-cell activity, teplizumab may help preserve the remaining beta cells and extend the period of endogenous insulin production.[12,17]

However, the increased incidence of adverse events at higher doses of teplizumab raises concerns about the safety of long-term use of anti-CD3 monoclonal antibodies. The occurrence of cytokine release syndrome, a potentially life-threatening condition caused by an excessive immune response, underscores the need for careful monitoring and dose optimisation in patients receiving teplizumab. Additionally, the long-term immunosuppressive effects of anti-CD3 therapy could increase the risk of infections and malignancies, which are significant considerations in the chronic management of T1DM.[12,17]

Future studies should focus on optimising dosing regimens to balance the efficacy of anti-CD3 monoclonal antibodies with their safety profile. This could involve exploring lower doses, alternative dosing schedules, or combination therapies that allow for reduced doses of teplizumab while maintaining its therapeutic effects. Additionally, identifying biomarkers that

predict patient response to anti-CD3 therapy could help tailor treatment to those most likely to benefit, thereby minimising unnecessary exposure to potential risks.

Combination therapies

The use of combination therapies in T1DM aims to target multiple aspects of the immune response simultaneously. The rationale behind combination therapies is that by addressing different pathways involved in the autoimmune destruction of beta cells, it may be possible to achieve more robust and sustained preservation of beta-cell function. The results of this review indicate that while some combination therapies, such as ATG and GCSF, have shown potential in preserving beta-cell function, the overall benefits have been inconsistent.[4,19]

The variability in the efficacy of combination therapies may be due to differences in study design, patient populations, and the specific combinations of agents used. For example, the combination of azathioprine and thymostimulin was found to improve long-term remission rates in some patients, but not all studies have replicated these findings. Moreover, the potential for increased adverse events with combination therapies is a significant concern, as combining multiple immunosuppressive agents could amplify the risk of side effects, including infections, malignancies, and organ toxicity.[19]

Further research is needed to identify the most effective combinations and dosing regimens for T1DM. This could involve conducting larger, multicentre trials with longer follow-up periods to assess the long-term efficacy and safety of combination therapies. Additionally, studies should explore the potential for combining immunosuppressive therapies with other treatment modalities, such as beta-cell regeneration or immune tolerance induction, to enhance their therapeutic effects while minimising risks.[18]

Novel immunotherapies and cytokine modulation

The development of novel immunotherapies targeting specific immune pathways represents an exciting avenue for T1DM treatment. These therapies aim to modulate the immune response in a more targeted manner, potentially reducing the autoimmune destruction of beta cells while minimising the broader immunosuppressive effects seen with traditional therapies.[10] Studies on cytokine modulation, such as IL-6 and IL-21 antagonists, have yielded mixed results, suggesting that while these approaches have potential, they are not yet fully understood.[22,23]

The success of DiaPep277 in preserving insulin production by altering cytokine profiles highlights the importance of understanding the immune mechanisms involved in T1DM. However, the variability in patient responses and the lack of consistent long-term benefits in subsequent studies underscore the challenges of developing effective immunotherapies for T1DM. The immune system's complexity and the multifactorial nature of T1DM suggest that a single-target approach may be insufficient to achieve long-term remission. Instead, combination therapies that address multiple aspects of the immune response may be necessary to improve outcomes.[21]

Future research should focus on identifying biomarkers that can predict response to these novel therapies and tailoring treatment accordingly. This personalised medicine approach could help identify patients most likely to benefit from specific immunotherapies, thereby improving their efficacy and reducing unnecessary exposure to potential risks. Additionally, exploring the potential for combining novel immunotherapies with existing treatment modalities, such as insulin therapy or beta-cell regeneration, could enhance their therapeutic effects and provide a more comprehensive approach to T1DM management.[22]

Conclusion

Immunosuppressive therapies offer potential benefits in managing T1DM by preserving beta-cell function and reducing insulin dependency. However, the current evidence indicates that these therapies are not yet capable of altering the long-term progression of the disease. The variability in patient responses and the challenges associated with long-term safety highlight the need for personalised medicine approaches in T1DM treatment. Future research should focus on identifying specific patient subgroups that are most likely to benefit from immunosuppressive therapies, optimising dosing regimens to balance efficacy and safety, and integrating these therapies with advanced diabetes management technologies.[10]

This systematic review underscores the importance of a multidisciplinary approach to T1DM management, combining immunosuppressive therapies with cutting-edge technologies and personalised medicine to improve outcomes for individuals affected by this autoimmune condition. By advancing our understanding of the immune mechanisms underlying T1DM and developing more targeted and effective therapies, it may be possible to alter the course of the disease and improve the quality of life for millions of individuals living with T1DM.[8]

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