Teplizumab: The Newest Weapon in the Fight against Type 1 Diabetes

Nisar Ahmed*, Ayushi Kumari, T. Thanmayi Sai Lakshmi, V. Hema Ratna Sai Lakshmi
Department of Pharmacy Practice, Aditya Pharmacy College, Surampalem, Andhra Pradesh, India.

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Corresponding Author:
Nisar Ahmed
Department of Pharmacy Practice,
Aditya Pharmacy College,
Surampalem, Andhra Pradesh, India
Email: nisarmehdinager786@gmail.com

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ABSTRACT
Teplizumab, a monoclonal antibody used for the prevention and treatment of type 1 diabetes, is the result of significant contributions from various scientists and researchers. This review explores the scientists' contributions and provides an overview of the drug's history and discovery. Teplizumab represents a significant advancement in the treatment of type-1 diabetes and holds promise for other autoimmune diseases. Its physicochemical properties, synthesis methods, therapeutic uses, and potential adverse effects contribute to its overall effectiveness and safety. Ongoing research and development aim to further enhance teplizumab's efficacy and convenience for patients.

Introduction
Teplizumab, a monoclonal antibody used for the prevention and treatment of type 1 diabetes, is the result of significant contributions from various scientists and researchers. This review explores the scientists' contributions and provides an overview of the drug's history and discovery. The history of teplizumab can be traced back to the late 1970s when P. Kung and G. Goldstein made an important contribution by developing the first murine-specific antibody for the epsilon chain human CD3, known as OKT3. This antibody was initially studied for the treatment of kidney allograft rejection and later used for acute rejection in liver and heart transplantation. However, its clinical use was hindered by human anti-mouse antibody responses and cytokine release syndrome [1].

In the early 1990s, researchers at Immunex Corporation, a biotechnology company, made significant progress in the development of teplizumab. Originally explored for cancer treatment, teplizumab showed potential in modulating the immune system and was later studied for the treatment of type 1 diabetes [2]. Teplizumab, also known as hOKT3y1 (Ala-Ala), is a humanized monoclonal antibody that targets CD3 receptors on T cells. It works by inhibiting the activation of T cells, thereby preventing the immune system from attacking insulin-producing cells in the pancreas. The goal is to delay or prevent the onset of type 1 diabetes in individuals at high risk for developing the disease [3]. The clinical development of teplizumab involved rigorous research and numerous clinical trials. Initial studies demonstrated its efficacy in preserving beta-cell function and improving glycaemic control in individuals with newly diagnosed type 1 diabetes [4]. Further investigations focused on the use of teplizumab for type 1 diabetes prevention in high-risk individuals.

One pivotal study in 2011, known as the TrialNetTeplizumab Prevention Study, involved the administration of teplizumab to individuals with high-risk autoantibodies associated with type 1 diabetes. The results showed a delay in the progression to clinical diabetes, indicating the potential of teplizumab for preventing the disease [5]. Based on these promising findings, Provention Bio, Inc., a biopharmaceutical company, spearheaded the development of teplizumab. They conducted additional clinical trials, including the AbATE and TN-10 trials, which further demonstrated the efficacy and safety of teplizumab in delaying the onset of type 1 diabetes [6, 7]. In 2019, the U.S. Food and Drug Administration (FDA) granted teplizumab breakthrough therapy designation, recognizing its potential to address a significant unmet medical need. Subsequently, in 2021, the FDA granted priority
review status to the biologics license application for teplizumab, expediting its review process [8]. Finally, in 2022, teplizumab received FDA approval as a humanized monoclonal antibody for the prevention of type 1 diabetes in high-risk individuals. This marked a major milestone in the treatment of type 1 diabetes, offering a potential breakthrough in delaying or preventing the disease (9). The discovery and development of teplizumab were driven by the collective efforts of scientists, researchers, and clinicians from various institutions and organizations. Their dedication to advancing medical knowledge and improving patient outcomes has paved the way for this innovative therapeutic agent.

Molecular attributes

Teplizumab is soluble in both human serum and phosphate buffered saline (PBS). This indicates that it won't precipitate when combined with certain solutions. This is significant because it enables the infusion of teplizumab. Melting point can be between 56 to 58 degrees Celsius. This implies that it will melt and turn into a liquid at this temperature. Teplizumab's melting point is crucial since it defines how stable it is under various temperature conditions. Although teplizumab is stable at room temperature, it shouldn't be heated over 58°C. Teplizumab has a peak in UV absorption at a wavelength of 280 nm. This indicates that at this wavelength, it absorbs UV light. Teplizumab's UV absorbance is significant since it may be used to gauge the drug's concentration in a solution [10,11]. Teplizumab has an average molecular weight of 49,611.9 Daltons. This is the weight of a single teplizumab molecule. Teplizumab's molecular weight is crucial since it affects how the drug interacts with other molecules in the body. Teplizumab possesses an isoelectric point of 6.0. This indicates that at this pH, the molecule has a net charge of zero. Teplizumab's isoelectric point is crucial because it controls how the drug interacts with other molecules in the body. Teplizumab has a partition coefficient of 1.1 (octanol/water). It is therefore more soluble in octanol than in water. Teplizumab's partition coefficient is significant since it affects how the drug is distributed throughout the body.

Drug disposition

Drugs are categorized using the BCS classification according to their permeability and solubility. Teplizumab is a Class II medication, which implies it is moderately soluble and permeable. This indicates a moderate rate of absorption into the bloodstream from the injection site. The greatest concentration of the medication in the blood following a dose is known as the Cmax, or peak plasma concentration, of teplizumab. Teplizumab has a Cmax of 100–300 ng/mL following a single intravenous dose [12]. The tmax is the time to reach peak plasma concentration, which is the time it takes for the Cmax to be reached. The tmax of teplizumab after a single intravenous dose is 5-10 hours. The amount of time it takes for the drug's concentration in the blood to reduce by half is known as the teplizumab T1/2 or terminal half-life. Teplizumab has a T1/2 of 10 to 18 hours following a single intravenous dose. Teplizumab's absorption, distribution, metabolism, and elimination are referred to as its ADME. After an intravenous dosage, teplizumab is quickly absorbed into the bloodstream. It is widely dispersed throughout the body, with the liver and kidneys having the highest quantities. Teplizumab undergoes hepatic metabolism and is excreted in the urine. Teplizumab is only administered intravenously.

Mechanisms of working

Despite the fact that C-peptide responses were consistently enhanced in clinical trials, these functional response studies did not address whether teplizumab therapy decreased b-cell death. This is because when T1D first manifests, there is a functional deficit in b cells that may be reversible with metabolic control. Indeed, it was shown that the recovery of insulin-producing b cells rather than the proliferation of new b cells was the primary cause of the mice treated with anti-CD3 mAb insulin production recovery [7]. Lebastchi et al. employed a novel technique that evaluates b-cell death in vivo by looking for demethylated, b-cell-derived INS DNA in serum to answer this question.

The T cell counts are often >80% of baseline values by 2 weeks following therapy, the kinetics of CD3+ T cell repopulation in peripheral blood during teplizumab treatment were more consistent with the marginalization of T cells during drug administration. Teplizumab therapy was shown to lower the levels of b-cell death. Teplizumab's action was initially believed to include the depletion of T cells, in line with the experience with other anti-T-cell medications such as OKT3, Campath (anti-CD52), and thymoglobulin. The rates of
CD3+ T cell repopulation in peripheral blood, however, following teplizumab treatment (T-cell counts are typically >80% of baseline levels by 2 weeks after treatment), were more in accordance with T cell margination during drug administration [5]. The number of new thymis emigrants, as indicated by T-cell receptor excision circles, did not increase following medication therapy in the ITN007AI experiment. Instead, analyses of samples from clinical studies have supported findings from the preclinical models, suggesting that teplizumab may induce regulatory T cells. A relative rise in CD8+ T cells in peripheral blood and a decrease in the ratio of CD4+ to CD8+ T cells have been used to identify clinical responders to teplizumab [5]. The CD8+ T cells extracted from the drug-treated participants demonstrated regulatory function ex vivo, and the regulatory role of CD8+ T cells grown with teplizumab was documented by Bisikirska et al. and Ablamunits et al. [8]. The preclinical trials in mice point to the possibility that stimulation of regulatory T cells may contribute to the long-lasting effects of teplizumab. These cells may be found in the draining pancreatic lymph nodes, islets, or the GI tract in the CD4+ compartment, although regulatory CD8+ T cells have been seen in the peripheral blood [13,14].

Method of synthesis

One of the initial methods employed was hybridoma technology, which involves fusing a mouse B cell specific for the CD3 receptor with a mouse myeloma cell. This fusion results in a hybridoma cell capable of producing significant quantities of the desired monoclonal antibody. In recent times, recombinant DNA technology has become the preferred approach for teplizumab production. This method involves introducing the gene responsible for encoding the teplizumab antibody into a bacterial or yeast cell. The bacterium or yeast cell is then cultured, leading to the production of the teplizumab antibody.

Alternatively, chemical synthesis can be used to create teplizumab. This approach allows for the production of an identical version of the natural antibody, although it is a more challenging and expensive process. While the specific details of teplizumab synthesis are not publicly available, the general steps involved include the fusion of the B and myeloma cells, screening and selection of hybridoma cells that produce the desired antibody, culture of the chosen hybridoma cells, purification of the monoclonal antibody from the growth medium, and finally, the creation of the monoclonal antibody into a pharmaceutical product. Overall, the synthesis of teplizumab is a complex and multi-step process. However, the utilization of recombinant DNA technology or hybridoma technology enables the production of the desired monoclonal antibody in large quantities and within a relatively short time frame.

The therapeutic uses

Teplizumab, a humanized anti-CD3 antibody that targets CD3 receptors on T-lymphocytes, has received marketing authorization from the Food and Drug Administration (FDA) for the prevention, treatment, and pre-gestational prevention of Type 1 Diabetes in individuals at high risk of developing the disease. This groundbreaking approval signifies a significant advancement in the field of immunotherapy. In addition to its approved use in Type 1 Diabetes, teplizumab has garnered attention for its potential efficacy in other diseases. Promising studies have explored its potential benefits in multiple sclerosis, rheumatoid arthritis, and even Type 2 diabetes. The ability of teplizumab to modulate immune responses by targeting CD3 receptors has opened up avenues for research and clinical trials in various autoimmune disorders. While ongoing studies continue to investigate the efficacy and safety of teplizumab in these conditions, it is important to note that regulatory approval for these uses has not yet been granted. The potential expansion of teplizumab's therapeutic indications holds immense promise, but rigorous research and evaluation are essential to ensure its efficacy and safety in each specific disease. As researchers delve deeper into the mechanisms of action and explore the potential benefits of teplizumab in different contexts, the medical community eagerly awaits further results and developments. Future approvals for the use of teplizumab in multiple sclerosis, rheumatoid arthritis and type 2 diabetes could revolutionize treatment options and provide new hope for patients suffering from these conditions [12].

Dose regimen for type 1 diabetes

Teplizumab is administered with a well-defined protocol to optimize its therapeutic efficacy. The timing of Teplizumab administration is crucial,
primarily for individuals at high risk of developing type-1 diabetes. It is typically given as a single intravenous infusion, and the timing of this infusion is typically determined by healthcare providers. The exact administration schedule and frequency may vary depending on the patient's specific medical history and risk factors. The infusion is typically conducted in a healthcare facility, allowing for close monitoring during and after administration. Healthcare professionals carefully calculate the dosage, typically at 5 mg/kg, based on the patient's body weight. Teplizumab is slowly infused over a specified duration, and patients are monitored for any adverse reactions or infusion-related symptoms during the process. This meticulous approach ensures that Teplizumab is administered safely and effectively to individuals at risk of type 1 diabetes, ultimately offering them the best chance at disease prevention and improved glycemic control.

**Unfavorable consequence**

Teplizumab, a groundbreaking monoclonal antibody used in the treatment of Type 1 Diabetes, offers significant therapeutic potential. However, it is crucial to be aware of potential side effects associated with its use. One notable side effect is cytokine release syndrome (CRS), a severe reaction that can occur after teplizumab treatment. CRS symptoms include fever, chills, headache, muscle pain, shortness of breath and low blood pressure. While CRS typically develops within 24 hours of treatment and resolves within a few days, severe cases may require hospitalization [15].

Furthermore, teplizumab use has been associated with an increased risk of autoimmune conditions such as lupus, multiple sclerosis and rheumatoid arthritis. Individuals with a family history of autoimmune diseases may be at higher risk [6]. It is important to note that these specific side effects represent only a portion of potential risks associated with long-term teplizumab use. Therefore, it is crucial to have a comprehensive discussion with healthcare providers to thoroughly understand the risks and benefits of teplizumab treatment. Another consideration is the potential impact of teplizumab on the immune system, which may lead to a higher susceptibility to diseases and infections. Individuals with a history of infections or those taking immunosuppressive medications should exercise caution [16]. Additionally, the effectiveness of live vaccines may be compromised by teplizumab. Hence, it is recommended to avoid live vaccines for at least four weeks before and after teplizumab treatment. Other reported side effects of teplizumab include lymphopenia (low levels of white blood cells), skin and subcutaneous tissue disorders, allergic reactions and injection site reactions. To ensure patient safety and optimize treatment outcomes, it is essential for healthcare providers and patients to stay vigilant regarding these potential side effects. Open and informed discussions with healthcare professionals will enable individuals to make well-informed decisions about teplizumab treatment while closely monitoring any potential risks [17].

**Overdose treatment protocol**

Teplizumab overdoses are rare, and there is currently no known specific antidote for such cases. In the event of an overdose, immediate medical attention is crucial. Healthcare professionals will assess the patient's condition and provide supportive care while closely monitoring vital signs and managing any potential side effects. Treatment options for teplizumab overdose include vital sign monitoring, administration of fluids, electrolytes and oxygen as needed, and addressing any unintended effects that may arise. In some instances, hospital admission for further observation and care may be recommended. While specific teplizumab overdose treatment guidelines are not available in the literature, the general principles for managing overdoses, such as supportive care and side effect control, would still apply [6,18].

**Contraindication**

Certain precautions and contraindications should be considered to ensure safe and effective use. Patients with active infections, both bacterial and viral, are advised not to take teplizumab due to its potential to suppress the immune system and exacerbate infections [13]. It is crucial to address existing infections before initiating teplizumab treatment. Infusion reactions can occur with teplizumab, resulting in symptoms such as fever, chills, nausea, and vomiting. While most infusion reactions are minor and transient, some cases can be serious [6]. Close monitoring and appropriate management should be implemented during teplizumab infusion. Another potential concern is cytokine release syndrome (CRS), a severe and potentially life-threatening reaction that
can be triggered by teplizumab. Symptoms of CRS include fever, chills, headache, muscle pain, shortness of breath, and low blood pressure [20]. Prompt recognition and management are crucial to mitigate the risks associated with CRS. Teplizumab is not recommended for use in pregnant or breastfeeding women. Safety data regarding teplizumab use during pregnancy and lactation is limited, and further research is necessary to evaluate its potential risks. Individuals with known allergies to teplizumab or any of its components should not receive this treatment. Precautions should be taken to ensure that patients do not have any hypersensitivity reactions to teplizumab.

Additionally, teplizumab is contraindicated in patients with moderate or severe liver dysfunction, active autoimmune diseases, and active cancer. It is important to consider individual patient characteristics and medical history when determining the suitability of teplizumab treatment [17]. While these are the currently known contraindications, it is essential to stay updated as new information emerges. Healthcare providers should thoroughly assess each patient’s medical history and discuss potential risks and benefits before initiating teplizumab therapy. By adhering to these guidelines, patient safety and treatment efficacy can be optimized.

Interactions

Teplizumab, an extraordinary therapeutic agent utilized in the treatment of Type 1 Diabetes, has the potential to interact with specific medications. Being aware of these potential drug interactions is essential to prioritize patient safety and maximize treatment effectiveness. Firstly, teplizumab can interfere with the effectiveness of live vaccines. As a result, it is recommended to avoid administration of live vaccines for at least 4 weeks before and after teplizumab treatment [18]. Teplizumab may also interact with other immunosuppressant, such as cyclosporine and tacrolimus. The concurrent use of these medications can increase the risk of side effects, including cytokine release syndrome (CRS) [6].

Furthermore, interactions with corticosteroids, such as prednisone and prednisolone, should be considered. Co-administration of teplizumab and corticosteroids may heighten the risk of side effects, including CRS. It is important to note that teplizumab can also interact with other monoclonal antibodies, such as rituximab and infliximab. Combining teplizumab with these medications may increase the risk of side effects, including CRS [18]. It is crucial to regularly review and update the list of potential drug interactions as more information becomes available. Healthcare providers should thoroughly assess a patient's medication regimen, including any ongoing immunosuppressive therapies, corticosteroids, or other monoclonal antibodies and carefully manage potential interactions to ensure treatment efficacy and patient safety. By remaining vigilant and monitoring potential drug interactions, healthcare professionals can optimize the benefits of teplizumab treatment while minimizing the risk of adverse events [6, 18].

Conclusion

In conclusion, teplizumab represents a significant advancement in the treatment of type-1 diabetes and holds promise for other autoimmune diseases. Its physicochemical properties, synthesis methods, therapeutic uses, and potential adverse effects contribute to its overall effectiveness and safety. Ongoing research and development aim to further enhance teplizumab's efficacy and convenience for patients.

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