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Pharmacodynamic and Pharmacokinetic Properties of Monoclonal Antibody: Teplizumab

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Abstract

Teplizumab, also referred as humanized monoclonal antibody, first developed in Columbia University, and later improved at MacroGenics, to have Fc receptor non-binding properties to reduce the incidence of CRS, was introduced to slow down stage 3 of type 1 diabetes mellitus. The US FDA in November 2022 approved this drug for the first time for type 1 diabetes mellitus. This article reviews summary of pathogenesis of type 1 diabetes mellitus, mechanism of action, pharmacodynamics, pharmacokinetics, efficacy, and safety of Teplizumab. In type 1 diabetes mellitus, autoantibodies were produced by immune cells against pancreatic beta cells leading to the depletion of pancreatic beta cells, the only insulin producing cells. After which, the patient has to be purely dependent on exogenous insulin injections to maintain normal blood sugar levels, which is essential for survival. Anti CD3 therapy has been used traditionally in organ transplantation, but more recently been tried in type 1 diabetes mellitus patients. Since Teplizumab is a newer version of CD3 monoclonal antibody, the clinical data on its pharmacodynamics and pharmacokinetic properties were limited. C peptide is a substance formed when the hormone insulin is produced and released into the body, so, measuring C peptide is an accurate way to find out how much insulin is produced. Both Phase 2 and 3 studies were revealed on C peptide to make sure the insulin production is adequate. In type 1 diabetes mellitus patients, 12 to 14 day Teplizumab infusion showed an improved glycemic control. Initial studies showed that Teplizumab was well tolerated. The only adverse effect is self-limited rash.

Keywords: Monoclonal Antibody; Type 1 Diabetes Mellitus; Pharmacodynamics; Pharmacokinetics

Abbreviation: DCCT: Diabetes Control and Complications Trial.

Introduction

Autoantibodies mediate type 1 diabetes mellitus and there is no way to protect the beta cells' destruction by the effector T cells. Pancreatic beta cells are the only cells, which produce insulin and maintain blood glucose under control. When a susceptible person develops type1 diabetes, the autoimmune T lymphocytes kills the pancreatic beta cells. There is depletion in mass as well as function. They are no longer able to produce the insulin hormone [1-3]. Type 1 diabetes mellitus patients depend on external insulin for

survival. Gene therapies were tried in the past, focused to produce new islets of beta cells to replace those that had been destroyed by autoimmune T lymphocytes. The prime aim of the research is to restore normal beta cell mass in the hope of accomplishing normal insulin production. Multiple therapeutic strategies had been tried for the production of new beta cells in place of those that have been destroyed by autoantibodies. However, it has been observed that the autoimmune T cells destroy the newly formed beta cells as well. Hence, a successful islet conservation therapy supported by a potent immunotherapy was tried, which will protect the newly formed beta cells from autoimmune T cells. Plethora of clinical trials using autoimmune antibodies and immune modifying medicines have been tried though most have proven to be either too toxic or have failed to provide beta cell protection from the autoimmune T cells [4].

Monoclonal Antibodies

Type 1 diabetes is generally considered as a disease of rapid onset. However, its development is a much slower process, because both genetic and environmental triggers must be there that causes invasion of pancreatic islets by T lymphocytes leading to beta cell destruction. The clinical symptoms usually develop after about 80% of pancreatic beta cells have been destroyed and the patient at that time is purely dependent on external insulin. In type 1 diabetes mellitus, the general conclusion is that though there is an autoimmune mechanism, it may not be the only true cause. Type 1 diabetes precipitates not only in genetically susceptible individuals, but it is also aggravated by environmental triggers as well. The following genes are known to be susceptible ones: Human Leukocyte Antigen (HLA) class II genes, insulin gene encoded on the chromosome 11p15, Protein Tyrosine Phosphatase, Non-Receptor type 22 (PTPN22), Interleukin 2 Receptor Subunit Alpha (IL2Ra), and Cytotoxic T Lymphocyte Associated Antigen protein 4 (CTLA4). There are also a number of viruses that have been linked to type 1 diabetes, including enters virus, Coxsackievirus B, rotavirus, mumps virus, and cytomegalovirus. The beta cell destruction done through the immune system by its components including B lymphocytes, macrophages, dendritic cells, antigen presenting cells, CD4+ T cells, CD8+ T cells, and natural killer cells [5].

Monoclonal antibodies are artificial proteins that mimic human antibodies in the immune system. There are four different ways they can be made, and are named accordingly.

- **Murine:** These are made from mouse proteins, and the names of the products ends with-omab.
- **Chimeric:** These proteins are made by fusing mouse and human proteins, and the names of the products end with-ximab.
- **Humanized:** These are made from small elements of mouse proteins combined with human proteins, and the names of the products end with -zumab (like Teplizumab).
- **Human:** These are fully human proteins, and the name of the products ends with–umab [6].

Pathogenesis of Type 1 Diabetes and Mechanism of Action of Teplizumab

Phase I: The starting phase of type 1 diabetes mellitus involves beta cell death through genetic and environmental triggers and activation of antigen presenting cells.

Phase II: This phase involves auto antigens and specific diabetogenic T cells, relocation of activated conventional dendrite cells; these dendrite cells further advance multiplication of regulatory T cells through the mass production of interleukin 10, indoleamine 2, 3-dioxygenase, transforming growth factor- beta, and inducible T cell co-stimulator ligand.

Phase III: This phase involves killing of beta cells by T cells and natural killer cells through the release of interferon gamma, granzymes, perforin, as well as by macrophages through the release of tumor necrosis factor, interleukin gamma -1 beta, and nitric oxide. Interleukin 12 produced by conventional dendritic cells stops the effector T cell functions and natural killer cells function. T regulatory cells prevent beta cell damage through interleukin 10 and transforming growth factor beta. Tolerogenic plasmacytoid dendritic cells stimulated by invariant natural killer cells could also control diabetogenic T cells through indoleamine 2,3–dioxygenase production. Lastly, beta cells can inhibit diabetogenic T cells by expressing periodontal ligament cell and escape the cell death [7].

Let us briefly explain the pathogenesis. First, the beta cells are damaged and insulin production starts to reduce. The person may not be aware of events and symptomatically, may be normal. Second, mutations in genes and environmental trigger factors as mentioned above cause the individual to develop type 1 diabetes mellitus by causing damage to the beta cells. These mutations in genetics and environmental trigger factors stimulate the cytokines, interferon alpha and major histocompatibility complex class I. They stimulate the auto-reactive CD8+ T lymphocytes to attack pancreatic beta cells. Third, the destroyed beta cells produce antigens. The antigen presenting cells pick up these antigens and transfer them to the lymph nodes. Fourth, the environmental trigger has caused a sudden stimulation of pro-inflammatory mediators like tumor necrosis factor and interferon gamma, and other pro-inflammatory mediators like interleukin 2 to 4, 6, and 10, and granulocyte – macrophage colony stimulating factor. They stimulate the effector T cell function

(degeneration) and reduce the regulatory T lymphocytes' function (proliferation) [8].

Beta cell antigens presented with these pro-inflammatory factors and CD4+ T lymphocytes help to initiate the reorganization of B cells into plasma cells and then they are switched to insulin autoantibodies. Fifth, this event eventually stimulates the auto-reactive CD8+ T lymphocytes to escalate and migrate into the pancreas. This stress mediates beta cell damage through perforins, interferon gamma, and tumor necrosis factor alpha. These responses cause more beta cells' death and decrease in insulin production. Sixth, the damaged beta cells also release new antigens, which are picked up by antigen presenting cells. Seventh, the migrated B cells reach the pancreatic lymph node. This response captures a new group of CD4+ and CD8+ T lymphocytes and B cells in a process called epitope spreading. A more vigorous wave of beta cell damage occurs because of this, which is more acute and usually ends in much exhaustion of beta cell mass and its function. Eight, interestingly, the autoimmune activation can also boost beta cell proliferation, so that the beta cell mass temporarily proliferates back to normal. Also, regulatory T cells can sometimes be overpowered and decelerate the effect of T effector response. There is an escalation between destructive and proliferative responses. The swing between attack by effector cells and immune modulation by regulatory cells ends up with beta cell damage and proliferation back to normal and the cycle continuous. Finally, the auto regulatory response wins though only 10 to 30% of functional beta cells remain. The clinically diagnosed phase of diabetes is known as honeymoon phase, which is a temporary state of self-effacing insulin production [8].

One of the important classes of biologic immune modulators composed of antibodies that target receptors on T cells were tried. Anti-CD3, monoclonal antibodies' like Teplizumab acts at different levels. They cause a short-term evident of T cell receptor-CD3 complex that makes the cell docking attack by antigens. Also, they alter T cell receptor-mediated signal transduction [9]. Out of these, apoptosis occurs preferentially in activated T helper 1 cell. This apoptosis is partially mediated by CD95-CD95L (Fas/APO-1/TNFRSF6) interactions with adjoining T cells. This explanation might prove why effector T cell apoptosis is more dramatic at the site of inflammation where the effector T cell density is highest. In addition, anti-CD3 treatment also results in regulatory T cell proliferation. It is believed that the regulatory T cells might protect the beta cells against damage by the effector T cells long even after the drug has been eliminated from the body. There is no necessary for a continuous immunosuppression, as there is appearance of the self- toleration. In human clinical trials, a reduction in the CD4+ and CD8+ ratio has been noted. The change in the ratio is not due to the depletion of CD4 cells but due to increase in regulatory Foxp 3 with CD 25 and CD8 and T cells while maintaining CD4+ T cells, thus leading to reduction in the ratio of CD4+ to CD8+ T cells [10].

Pharmacodynamics of Teplizumab

Teplizumab is a humanized monoclonal antibody that binds to both CD4+ and CD8+ effector T cells' surface CD3 molecules, which were involved in the destruction of pancreatic beta cells. Multiple studies showed an increase in C-peptide levels in early onset type1 diabetes patients treated with Teplizumab, suggesting an augmented beta cell function. Pharmacodynamic adverse effects of Teplizumab include lymphopenia, rash, leukopenia, and headache. In pregnancy, it is teratogenic. A lactating woman may consider pumping and discarding milk during and 20 days after Teplizumab intake (Figure 1) [11].

Pharmacokinetics of Teplizumab

Protein Chemical Formula

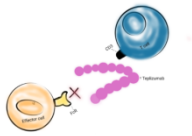

Figure 1: Protein Chemical Formula: C6462H9938O2022S46.

The Structural Formula

Teplizumab is a humanized version of mouse monoclonal OKT3 antibody retaining the same binding region of OKT3, but with amino acids at position 234 and 235 of the human IgG1 Fc changed to alanine resulting in decreased Fc binding [12].

The Heavy Chain

QVQLVQSGGG VVQPGRSLRL SCKASGYTFT RYTMHWVRQA PGKGLEWIGYINPSRGYTNY NQKVKDRFTI SRDNSKNTAF LQMDSLRPED TGVYFCARYY

DDHYCLDYWG QGTPVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKDYFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY

ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPEAAGGP SVFLFPPKPKDTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS

TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQVYTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL

DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGK.

The Light Chain

DIQMTQSPSS LSASVGDRVT ITCSASSSVS YMNWYQQTPG KAPKRWIYDTSKLASGVPSR FSGSGSGTDY TFTISSLQPE DIATYYCQQW SSNPFTFGQG
TKLQITRTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVDNALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL
SSPVTKSFNR GEC.

Disulfide Bridges Location

22-96 22''-96'' 23'-87' 23'''-87''' 133'-193' 133'''-193''' 146-202 146''-202''
213'-222 213'''-222'' 228-228'' 231-231'' 263-323 263''-323'' 369-427 369''-427''T.

Teplizumab's average weight seems to be 150000.0 Daltons, and its volume of distribution seems to be 2.27 Liters. As a monoclonal antibody, its clearance is not dose dependent. Teplizumab might be metabolized by catabolic pathways into small peptides throughout the body. Its mean elimination half-life is 4 to 5 days, has a clearance of 2.7 liters per day. Being new, toxicity information about Teplizumab is not readily available. Patients with overdosage experience an increased risk of severe adverse effects such as serious infections, lymphopenia, and cytokine release syndrom, symptomatic and supportive measures are recommended for those. As an antibody, Teplizumab is not expected to interact directly with DNA. Teplizumab did not have significant effects in the fertility and reproductive performances when administered subcutaneously at doses up to 20 mg/kg to male and female mice. No drug-food interactions were found [13,14].

Conclusion

It has been found that Teplizumab, a promising newer generation CD3 molecule, which is now available in the market, improves the condition of patients with type 1 diabetes mellitus found to be delaying the disease process. A 12 to 14 day course of Teplizumab therapy resulted in a stable beta cell function during the first year after treatment and a gradual decline in the second year. C-peptide levels are higher in the treatment group than in the control group at all time. Current clinical trials are administering two courses of drugs, one at the time of diagnosis and the other after six months. Adverse events reported seem to be mild and of short duration. Fever, headaches, myalgia, nausea and vomiting, and pruritic rash are the commonest reactions. All the patients have lymphopenia, which recovers at about 1 month. A case of thrombocytopenia was reported [15,16].

The treated patients have better glucose control and lower insulin requirements even though the drug does not completely arrest the damage in beta cell function. The Diabetes Control and Complications Trial (DCCT) showed that having some beta cell function is associated with lower risk of hypoglycemia; better glycemic control; and lower rate of microvascular complications. Long term follow up of the DCCT cohort also showed what is referred to as the legacy effect - that is tight control at first translates into lower risk for microvascular complications even if control deteriorates at a later date. Thus, decreasing the rate of decline in beta cell function may translate into improved glycemic control with less risk of hypoglycemia and lower incidence of long term complications. Measuring autoantibodies against beta cell antigen is now possible by HLA typing; and measuring first phase insulin secretion to identify individuals who are at 35 to 60 % 5 year risk for the development of type 1 diabetes mellitus. If long term safety issues are resolved, then it is likely that immune therapies like Teplizumab will be used in at risk individuals to arrest the disease at an early stage and prevent the development of diabetes.

References

1. US Food and Drug Administration. FDA.
2. (2023) Teplizumab (Tzield) to delay onset of type 1 diabetes. Med Lett Drugs Ther 65(1667): 7-8.
3. Harold KC, Bundy BN, Long SA, Bluestone JA, Di Meglio LA, et al. (2019) An anti CD3 antibody, teplizumab in relatives at risk of type-1 diabetes. N Engl J Med 381(7): 603-613.
4. Lee HC, Cha BS, Nam MS, Song YD, Lim SK, et al. (1995) Relationships among 64k autoantibodies, pancreatic beta-cell function, HLA-DR antigens and HLA-DQ genes in patients with insulin-dependent diabetes mellitus in Korea. Korean J Intern Med 10(1): 1-9.
5. Sims EK, Bundy BN, Stier K, Serti E, Lim N, et al. (2021) Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals. Sci Transl Med 13(583): eabc8980.
6. Kung PC, Goldstein G, Reinherz EL, Schlossman SF (1979) Monoclonal antibodies defining distinctive human T cell surface antigens. Science 206(4416): 347-379.
7. Sherry N, Hagopian W, Ludvigsson J, Jain SM, Wahlen J, et al. (2011) Teplizumab for treatment of type 1 diabetes (Protégé study): 1-year results from a randomised, placebo-controlled trialLancet 378(9790): 487-497.
8. Vudattu NK, Herold KC (2014) Treatment of new onset type 1 diabetes with Teplizumab: success and pitfalls in development. Expert Opin Biol Ther 14(3): 377-385.
9. Daifotis AG, Koenig S, Chatenoud L, Herold KC (2013)

Anti CD3 clinical trials in type diabetes mellitus. Clin Immunol 149(3): 268-278.

10. Masharani UB, Becker J (2010) Teplizumab therapy for type 1 diabetes mellitus. Expert opin Biol Ther 10(3): 459-465.

11. Kuhn C, Weiner HL (2016) Therapeutic anti–CD3 monoclonal antibodies from bench to bedside. Immunotherapy 8(8): 889-906.

12. https://pdfs.semanticsscholar.org/1344/595989e5ea881fd587fca3c5e4bb8e057ca4.pdf.

13. Masharani UB, Becker J (2010) Teplizumab therapy for type 1 diabetes. Expert Opin Biol Ther 10(3): 459-465.

14. United States Adopted Name (USAN) Drug Finder. AMA.

15. (2019) Globant. Empowering organizations for a digital and cognitive revolution.

16. Lucier J, Weinstock RS (2023) Diabetes Mellitus–type 1. NIH.