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MONOGRAPH

TEPLIZUMAB

Rec INN; USAN

Anti-CD3 Human Monoclonal Antibody
Treatment of Diabetes

hOKT3γ1(Ala-Ala)
HuOKT3γ1(Ala234-Ala235)
MGA-031

Immunoglobulin G_1, anti-[human CD3 epsilon (CD3E)] humanized monoclonal antibody MGA031 [hOKT3γ1(Ala-Ala)]; γ_1 heavy chain 236L>A, 337L>A [humanized VH (*Homo sapiens* FR/*Mus musculus* CDR from clone OKT3)-*Homo sapiens* IGHG1*01, 117L>A (CH2 1.3), 118L>A (CH2 1.2)] (222-213)-disulfide with κ light chain [humanized V-KAPPA (*Homo sapiens* FR/*Mus musculus* CDR from clone OKT3)-*Homo sapiens* IGKC*01] ; (228-228': 231-231')-bisdisulfide dimer

Immunoglobulin G_1, anti-(human CD3 (antigen) ε-chain) (human-mouse monoclonal MGA031 heavy chain), disulfide with human-mouse monoclonal MGA031 light-chain, dimer

Immunoglobulin G_1, anti-(human T-cell surface glycoprotein CD3 ε chain) humanized mouse monoclonal MGA031; γ_1 heavy chain [humanized VH (*Homo sapiens* FR/*Mus musculus* CDR)-[117-alanine, 118-alanine]*Homo sapiens* IGHG1] (222-213')-disulfide with κ light chain [humanized V-KAPPA (*Homo sapiens* FR/*Mus musculus* CDR)-*Homo sapiens* IGKC]; (228-228'':231-231'')-bisdisulfide dimer

CAS: 876387-05-2
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SUMMARY

The escalating statistics seen worldwide for autoimmune type 1 diabetes threaten to overwhelm healthcare systems, and therefore the importance of novel therapeutic strategies for this syndrome is growing. Teplizumab (MGA-031) is a humanized Fc-mutated monoclonal antibody designed to target the CD3 T-cell surface antigen, shown to be involved in T-cell activation, in a bid to preserve or protect pancreatic β-cells, thus reducing insulin dependence. MacroGenics, in collaboration with Lilly, has successfully shown that teplizumab reduces autodestruction of insulin-producing islet β-cells in open-label, randomized phase I/II studies in newly diagnosed type 1 diabetics, with sustained responses achieved up to 2 years after treatment. These proof-of-concept studies have facilitated progression of this agent to the phase III Protégé trial, a randomized, double-blind, multicenter, multinational, four-arm, controlled study.

BACKGROUND

T-cell-mediated autoimmune diabetes (type 1; also referred to as juvenile or insulin-dependent diabetes) is characterized by the production of autoantibodies that target the insulin-secreting β-cells of the pancreas. This results in little or no insulin production and an inability to properly control blood glucose levels. The incidence of type 1 diabetes is growing; a population analysis conducted in 2002-2003 in the U.S. indicated that 15,000 youths are newly diagnosed with type 1 diabetes annually, with the rate of new cases at 19 per 100,000 each year (1). These escalating statistics are seen worldwide (2) and threaten to overwhelm healthcare systems, and therefore the importance of novel therapeutic strategies for this syndrome is growing.

Teplizumab (MGA-031) is a humanized Fc-mutated monoclonal antibody engineered to alter the function of the T lymphocytes that mediate the destruction of the insulin-producing β-cells of the islets of the pancreas. Teplizumab targets the CD3 T-cell surface antigen, which has been shown to be involved in T-cell activation. If teplizumab is effective and has the ability to preserve or protect β-cells of the pancreas, patients may require less injected insulin and their blood glucose levels may be easier to control. Teplizumab was developed as a result of toxicity issues (cytokine release syndrome) reported for its predecessor OKT3 (3) and it is currently undergoing clinical development by MacroGenics in collaboration with Lilly for the treatment of type 1 diabetes (4). Active trials are outlined in Table I.

CLINICAL STUDIES

Phase I/II trial data from randomized, open-label studies have analyzed the effect of teplizumab on loss of insulin production in patients with type 1 diabetes (N = 42). Within 6 weeks of diagnosis, subjects received either a single 12- or 14-day course of i.v. teplizumab administered over 15-30 min (n = 21) or no treatment (n = 21). The first 12 patients randomized to treatment in the study received escalating drug doses for 4 days followed by full dose for 10 days (45 μg/kg/day). The next 9 patients underwent a dosing change (+23%) due to the development of anti-idiotypic antibodies in the previous

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Table I. *Teplizumab active clinical trials in type 1 diabetes (updated May 31, 2010).*

Stage of development	Country	Company	Reference
Phase III	U.S.	MacroGenics, Lilly	5, 6
Phase II/III	U.S., Canada, Czech Republic, Estonia, Germany, India, Israel, Latvia, Mexico, Netherlands, Poland, Romania, Spain, Sweden, Ukraine, U.K.	MacroGenics	7
Phase II	U.S.	National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Allergy and Infectious Diseases (NIAID) Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) National Center for Research Resources (NCRR) Juvenile Diabetes Research Foundation American Diabetes Association	8
	U.S.	Yale University National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Juvenile Diabetes Research Foundation	9
	U.S.	National Institute of Allergy and Infectious Diseases (NIAID) Immune Tolerance Network	10
Phase I/II	U.S.	University of Minnesota - Clinical and Translational Science Institute National Institutes of Health (NIH) Juvenile Diabetes Research Foundation	11

12 patients upon completion of treatment. Patients were monitored for a total of 24 months at 3- to 6-month intervals, with no long-term drug-related adverse events. Mild yet controllable adverse events were reported during drug treatment, usually at administration of the full dose (fever, headache, myalgia and arthralgia). Teplizumab provided a significant beneficial effect when monitoring C-peptide responses to a mixed meal (a marker of β-cell function). C-peptide responses were preserved for 1 year after diagnosis (97% response versus 53% response for control subjects). These improvements were further extended to a 2-year observation of these subjects, with 67% of those receiving teplizumab having a stimulated C-peptide level of ≥ 0.2 pmol/mL (indicated by the Diabetes Control and Complications Trial to suggest improved metabolic control in patients with type 1 diabetes) versus 26% of control subjects. Glycated hemoglobin (HbA1c), a good indicator of hyperglycemia, levels were also reduced, with a significantly lower insulin dose required in the drug-treated group at months 6-24. There was little associated change in levels of anti-GAD65 or anti-CA512 autoantibodies, and while drug-treated subjects demonstrated a significant lowering of their insulin autoantibody indices at 12 months, this was not sustained into the second year of observation. These responses were associated with a significantly reduced ratio of $CD4^+$:$CD8^+$ T cells after 90 days of treatment (due to an increased $CD8^+$ count) (12-15).

An extended follow-up of patients from this phase I/II study has been carried out, but only in a small cohort of those receiving doses +23% of those administered initially. The more significant results emerging from this 5-year follow-up indicate a trend for maintained C-peptide responses (16).

The change in $CD8^+$ cells has been investigated further in cultures of peripheral blood mononuclear cells (PBMCs) isolated from whole blood samples taken from volunteer donors and participants of the phase I/II clinical trial. These studies identified a teplizumab-associated induction of $CD8^+$ regulatory T cells characterized by expression of CD25 and Foxp3 (17).

To minimize concerns regarding toxicity, the extent of associated cytokine release was determined in sera collected from subjects participating in the phase I/II study. Significant increases in interleukins IL-10 and IL-5 were shown during teplizumab treatment in the serum of 63% and 72% of patients, respectively. In contrast, TNF-α and IL-6 levels were lower than those previously reported following OKT3 therapy (18).

A multinational phase II/III clinical trial (N = 530 patients anticipated: Protégé study) has been initiated to assess the safety, tolerability and efficacy of teplizumab. This consists of an open-label first segment involving i.v. teplizumab administration for 14 days at study entry and at 6 months, and a randomized, double-blind, placebo-controlled second segment. Based on currently available data from segment 1 of this investigation (n = 37; mean age = 16.6 years), HbA1c levels were reduced to 6% at day 91 versus 7.3% pretreatment, with mean insulin use also decreasing from 0.43 units/kg/day pretreatment to 0.31 units/kg/day on day 91. Of the total 37 subjects

participating to date, only 1 has experienced a serious drug-related adverse event; the general safety profile has been reported to be acceptable (19).

Serum samples from the above clinical trials, blood donors and patients with type 1 diabetes have permitted further elucidation of the way in which teplizumab modifies human immune responses in type 1 diabetes. Analysis of antigen-specific $CD8^+$ T cells with class I MHC tetramers has indicated that teplizumab significantly increases the proportion of glutamic acid decarboxylase (GAD)- and insulin B chain (InsB)-specific $CD8^+$ T cells (20).

A single-center, prospective, open-label pilot study has shown that teplizumab-induced immunosuppression contributes to reversal of type 1 diabetes via single-donor islet transplantation (n = 6; teplizumab with sirolimus 2 days pretransplantation, followed by maintenance immunosuppression with tacrolimus). Despite significantly reduced sirolimus exposure, islet allograft rejection and autoimmune recurrence were avoided in those emerging as insulin-independent recipients. Teplizumab exposure was also related to inversion of $CD4^+$:$CD8^+$ ratios, elevated IL-10 levels (thought to promote the development of "protective" T-helper 2 cells) and a progressive increase in $CD4^+$ T cells expressing CD25 (regulatory T cells) (21).

SOURCE

MacroGenics, Inc. (US); developed in collaboration with Eli Lilly and Co. (US).

DISCLOSURES

The author states no conflicts of interest.

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