# Depleting T cells in newly diagnosed autoimmune (type 1) diabetes--are we getting anywhere?

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# Depleting T Cells in Newly Diagnosed Autoimmune (Type 1) Diabetes—Are We Getting Anywhere?

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Autoimmune, or type 1 diabetes (T1D), is increasing worldwide in parallel with increases in the global standard of living. Geographically, the prevalence and incidence are diverse, explained in part by the heterogeneous distribution of HLA genetic factors on chromosome 6 that control the body's way of dealing with infectious diseases. This may explain why some countries have a higher prevalence of T1D than others. Indeed, while Japan has relatively low levels of T1D, other countries such as Finland and Sweden are more heavily affected. The disease may affect a person at any age and the severity of the clinical onset loss of β-cells is highly variable (Fig. 1). As there are no screening programs for HLA risk and islet autoantibodies that predict the disease, the vast majority of T1D patients are not recognized until the day of clinical diagnosis (1,2).

At diagnosis, patients' β-cell function profile can vary depending on the loss of β-cells. Some younger patients may have lost essentially all β-cells and their function, while older patients may still have considerable endogenous insulin left, with their diabetes masquerading as type 2 (1). It has taken some 40 years of research to appreciate that juvenile diabetes, insulin-dependent diabetes, T1D, and latent autoimmune diabetes in the adult are the same thing. As Shakespeare noted "that which we call a rose/ By any other name would smell as sweet." What matters is what autoimmune diabetes is, not what it is called. T1D may manifest with variable loss of β-cells dependent on the function of the remaining β-cells and insulin sensitivity (Fig. 1). According to American Diabetes Association/World Health Organization criteria, T1D may become manifest in children aged 1–10 years when 20% of the β-cell mass remains. In 20–30–year-old patients, diabetes may appear as a combination of poor β-cell function and insulin resistance despite an adequate β-cell mass. Any clinical study that aims to recruit subjects with new-onset T1D between the ages of 8 and 35 years will face this well-known heterogeneity.

The past 30 years of clinical studies and trials with immunosuppressive drugs aimed at inhibiting or preventing immune activity have been informative. We have learned a lot about T1D after the point of clinical diagnosis. However, none of the numerous immunosuppressive agents that have been tested so far have come close to being used in the clinic, let alone to replace insulin that every T1D patient is dependent on for survival. The focus of current approaches is to induce immunological tolerance, to unwind the otherwise chronic autoimmunity against autoantigens, such as GAD65, insulin, IA-2, and ZnT8, rather than induce broad immunosuppression.

The article by Hagopian et al. (3) in this issue focuses on teplizumab, also known as hOKT3gamma1(Ala-Ala), a humanized, anti-CD3 monoclonal antibody provided by MacroGenics (Rockville, MD). Intravenous infusion of this monoclonal antibody in a smaller study of 58 patients showed preservation of residual C-peptide and reduced insulin dosage in some patients (4,5). The phase 3 trial in 516 patients aged 8–35 years was conducted at 83 clinical centers in North America, Europe, Israel, and India (6). The possibility of detecting mechanisms that may explain a possible preservation of β-cell function was somewhat diluted by three different treatment arms in addition to the placebo arm. The primary outcome was long-winded and somewhat surprising: the percentage of patients with insulin use of $<0.5$ units/kg/day and $HbA_{1c}$ of $<6.5\%$ at 1 year. This kind of end point would seem to be driven by commercial interests rather than by a distinct attempt to preserve β-cell function. None of the three treatment groups reached this end point after 1 year (6). The 1-year study was deemed a failure. Of 516 randomized patients, 513 were treated, and 462 completed the 2-year follow-up that is now reported (6).

There is a major question in conducting clinical studies and trials with immunosuppressive agents. When will

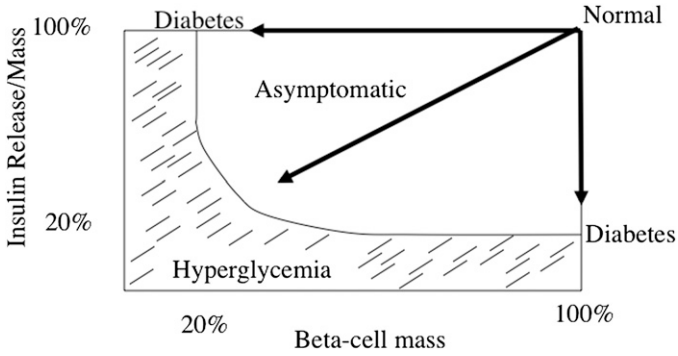


**FIG. 1. Relationship between insulin release in relation to the remaining β-cell mass. Research subjects entering an intervention trial at 8–35 years of age at the time of clinical diagnosis, such as the Protégé trial, may have vastly different baselines that may affect treatment and outcome. Subjects to the left may have lost a major proportion of their β-cells but still remain asymptomatic due to well-functioning β-cells and high insulin sensitivity. Subjects to the right may develop diabetes due to poor β-cell function and high insulin resistance. Heterogeneity already at baseline complicates immunomodulation intervention trials in T1D. The figure is courtesy of Daniel Cook and Ian Sweet, University of Washington, Seattle, Washington.**

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immunosuppressive treatments to preserve residual β-cell function surpass current insulin analogs, treatment approaches with pens and pumps, as well as continuous glucose monitoring in ways that approximate an artificial pancreas? The current study by Hagopian et al. (3) is no exception. As expected, there were significant dose-dependent adverse events and severe adverse events during the first year of follow-up (6). At least there were no *new* safety or tolerability issues observed during the second year. Long-term safety is a major issue in all studies with immunosuppressive agents and it will be critically important that patients who have been exposed to these agents are followed up long-term.

Phase 3 clinical trials have the advantage that a sufficient number of subjects may be exposed to the test agent to allow the investigator (less so the company that is hoping to put a drug on the market) to ask questions about possible responder populations. This was also the case in the 2-year follow-up of teplizumab-treated patients (3).

Several important points warrant comment. First, it was a brave move by MacroGenics to include clinics in India to participate. We all understand that it is less expensive to conduct a clinical trial in India. However, T1D diabetes etiology and pathogenesis is less well understood in India than in other countries. It was therefore somewhat surprising that the patients in India did not show β-cell preservation and reduction in insulin dose. This might have been because their disease was more advanced at the time of enrollment.

Second, all biologics have the problem that recipients develop antibodies against the drug. This is not new to patients with T1D who still develop antibodies against insulin and perhaps more so to insulin analogs. Antidrug antibodies also developed after teplizumab treatment but apparently without effects on outcome.

Third, prespecified and post hoc analyses of patient subsets revealed groups of subjects who were responders to teplizumab at 2 years post enrollment. These included U.S. residents and patients with C-peptide mean area under the curve >0.2 nmol/L who were randomized within 6 weeks after diagnosis with $HbA_{1c}$ <7.5% (58 mmol/mol) and with insulin use <0.4U/kg/day. Also, the greater teplizumab-associated C-peptide preservation was observed in patients 8–17 years of age, and seemed to indicate that younger patients were better responders than older ones.

Fourth, CD4+ and CD8+ T cells were transiently reduced during each cycle of high-dose treatment and there was some data that teplizumab was bound to peripheral blood T cells. The suggestion that teplizumab has to be given at a higher dose to achieve an effect on residual C-peptide is interesting from the point of view that higher dosages of this kind of biologic increases the risk for cytokine release syndrome. This syndrome may itself affect β-cell function and insulin resistance, thereby affecting residual β-cell function.

The study by Hagopian et al. (3) is important to future use of teplizumab and similar reagents in the quest to halt β-cell loss after the clinical onset of T1D. In this setting, it is important to lay all cards on the table and examine outcomes in relation to the subjects fulfilling the inclusion criteria. HLA genotypes and levels and number of islet autoantibodies, levels of insulin antibodies, T- and B-cell subsets, and monocyte/macrophage numbers need to be analyzed at baseline and during follow-up to better understand to what extent treatment affected these markers. Analyses of these types may predict T1D prognosis (7,8). Finally, the long-term experience in T1D clinical trials seems to be that monotherapy is less effective and informative than trials focused on combination therapy (9,10).

Investigators planning future studies of immunosuppressive agents to test the hypothesis that they are immunomodulating may want to include autoantigens such as insulin, GAD65, IA-2, and ZnT8 in the protocol (11). Treatment with insulin (perhaps proinsulin) and GAD65 (12) appear to be safe, and a combined administration of autoantigen may enhance specific Treg cells of the kind observed in response to teplizumab (3). The take-home message from the completed Protégé trial seems to be that there is more to the outcome of this study than sweeping statements suggesting a major failure because the so-called primary end point was not met.

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# AUTHOR QUERIES

## AUTHOR PLEASE ANSWER ALL QUERIES

Q1: Please provide a reference for the Shakespeare quote and renumber the references and confirm the reordering.

Q2: In the sentence beginning, "The primary outcome...," please confirm that the edited sentence reads as meant.

Q3: In the sentence beginning, "These included U.S. ...," please confirm that the edited sentence reads as meant.

Q4: In the sentence beginning, "Also, the greater...," please confirm that the edited sentence reads as meant.

Q5: Check that the conflict of interest information for each author is presented in full in the Acknowledgments section.