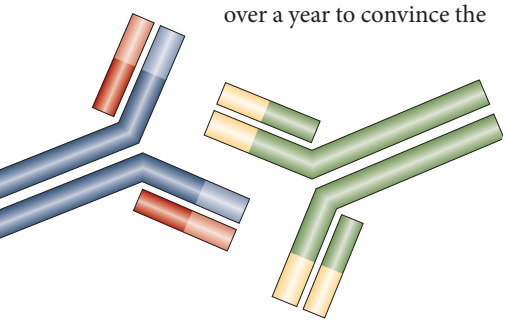
NONINSULIN THERAPIES FOR T1DM

Selective depletion of B lymphocytes with rituximab preserves β-cell function

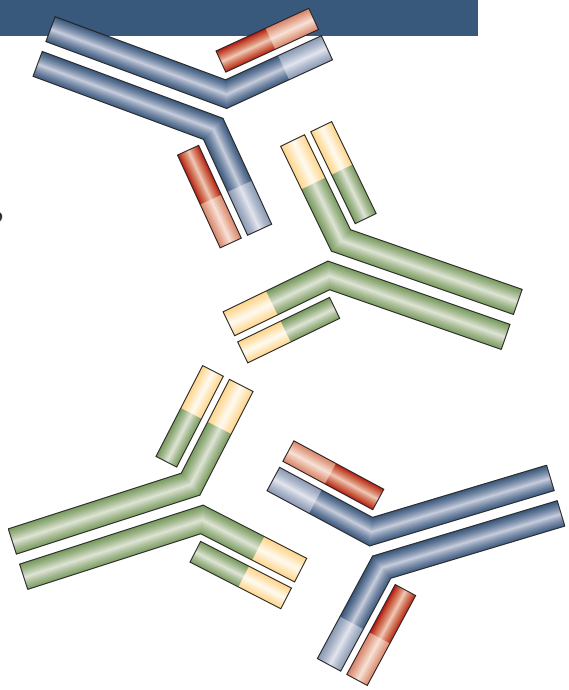
Selective depletion of B lymphocytes could represent a novel approach to the management of patients with newly diagnosed type 1 diabetes mellitus (T1DM), according to phase II data reported by the TrialNet Anti-CD20 Study Group. "The most significant finding is that a treatment that specifically targets B cells can lead to preservation of insulin secretion," explains lead researcher Mark Pescovitz, a transplant surgeon at the Indiana University School of Medicine in Indianapolis. "It now opens the field up to alternative therapies that target B cells, either as single agents or perhaps combined with other agents."

The progressive autoimmune destruction of pancreatic β cells characteristic of T1DM is widely believed to involve T lymphocytes. However, studies of the nonobese diabetic (NOD) mouse suggested that B lymphocytes might also play a part. Indeed, selective depletion of B lymphocytes prevented the onset of autoimmune diabetes in these mice. Pescovitz was aware that rituximab—a chimeric anti-CD20 monoclonal antibody developed to treat hematological neoplasias—had shown promise for the treatment of autoimmune diseases, such as rheumatoid arthritis. He, therefore, hypothesized that rituximab (which targets an antigen present on the cell surface of mature B lymphocytes) might be effective as a treatment for T1DM. "Initially, the idea was met with skepticism," says Pescovitz. "It took over a year to convince the TrialNet study group to move forward with a trial and it was not funded by some agencies for lack of belief in the concept."



Enrollment in the trial eventually commenced in May 2006. The study group included 87 patients aged 8–40 years with newly diagnosed T1DM who were treated at 12 centers in the US and Canada. The team randomly allocated the participants to receive either rituximab or placebo. The dosing schedule was based on the rituximab regimen originally used for cancer therapy and was selected by the researchers because it had already been used successfully in children. Patients received an infusion of either rituximab or placebo on days 1, 8, 15 and 22 of the study; the four infusions constituted a single course of treatment. The primary outcome measure was the mean area under the curve (AUC) for the stimulated C-peptide response during the first 2 h of a 4 h mixed-meal tolerance test. Secondary outcome measures included the HbA_{1c} level, insulin dose and rate of infusion-related adverse effects.

Treatment with rituximab led to a specific depletion of $CD19^+$ B lymphocytes, although these cells eventually rebounded to 69% of the baseline value. The mean AUC for the level of C-peptide at year 1 was around 20% higher in the group that received rituximab than in the control group. Treatment with rituximab was also associated with higher absolute levels of C-peptide at 3, 6 and 12 months after the first infusion. The decline in the C-peptide levels detected during follow-up was reduced in the rituximab group (37.7% versus 55.8% in the placebo group). Treatment with rituximab was also associated with lower HbA_{1c} levels and exogenous insulin requirements than were observed after infusion with placebo. Adverse events after the first infusion were more common among patients in the rituximab group than in the placebo group (93% versus 23%, respectively); the rate of adverse reactions was similar for subsequent infusions. Increased rates of infection and neutropenia were not reported by the rituximab group.



The results of this study suggest that selective depletion of B lymphocytes can preserve β-cell function in patients with new-onset T1DM. The next step is to optimize therapies that target B lymphocytes. "Such optimization could include additional dosing over time or the use of alternative anti-B-cell agents," Pescovitz suggests. "Furthermore, individuals at high risk of T1DM—those with autoantibodies but normal blood sugar levels—could be treated to actually prevent the development of T1DM." Such trials are already under development.

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