The Compelling Case for Anti-CD3 in Type 1 Diabetes

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Immunotherapy trials in recent-onset type 1 diabetes (T1D) have had mixed results, with some therapies—anti-CD3 monoclonal antibodies targeting T cells (1–7), anti-CD20 monoclonal antibodies targeting B cells (8), and costimulation blockade (9)—showing promise, with at least transient improvement in β-cell function compared with randomized control groups. In the current issue, Herold et al. (10) from the Immune Tolerance Network (ITN) report the results of the Autoimmunity-Blocking Antibody for Tolerance in Recently Diagnosed Type 1 Diabetes (AbATE) trial. This is the fifth trial with anti-CD3, the fourth with the monoclonal antibody teplizumab, demonstrating preservation of β-cell function.

The article describes a group of "responders" to treatment, identified by the label "responders" for those who maintained C-peptide better than the randomized but untreated comparison group at 24 months. Responders, defined in this way, constituted 45% of the subjects treated with anti-CD3. When examining β-cell function over time in the trial, it was evident that the responders had maintained β-cell function for 2 years, whereas the nonresponders had lost β-cell function at a rate similar to the control group. This is a crucial observation, because in an analysis that includes both responders and nonresponders, the profound retention of C-peptide in nearly half of subjects can be missed. The fundamental question is why some subjects failed to respond. It could be that the immunotherapy was ineffective (at least at the dose used), that the immunologic process—perhaps a relapsing and remitting one—was in a latent period at the time of drug administration, that β-cell mass or function had already deteriorated to a point of no return, that the immunologic processes damaging β-cells are different among individuals, or for some other reason.

It turns out that at baseline, prior to treatment, the responders had lower HbA_{1c} levels and used less insulin than the nonresponders. Unfortunately, there is not an unambiguous demarcation of HbA_{1c} level or of insulin dose to identify responders a priori, but rather there is overlap of HbA_{1c} levels and of insulin dose between responders and nonresponders. However, the lower HbA_{1c} levels and lower insulin doses imply that the responders may have had a milder disease or be earlier in the course of the disease, consistent with comments by Jean-Francois Bach (11) that: "Ideally, type 1 diabetes should be regarded as a medical emergency and treatment with teplizumab could be started within a few days after diagnosis, as compared with several weeks or months as is done now." It is also consistent with data from NOD mice that treatment with anti-CD3 is most effective around the time of disease onset (12). And it supports the notion that likely one of the best times to use anti-CD3 is at the stage of dysglycemia (i.e., glucose abnormalities that do not meet the current criteria for diagnosis of diabetes). Such a trial is currently being conducted by Type 1 Diabetes TrialNet (13). Subjects being enrolled in that trial have a projected 75–80% risk of T1D within 5 years, and all are expected to develop T1D within 10 years.

It is remarkable that the anti-CD3 monoclonal antibodies have shown remarkably few adverse events, most being transient at the time of infusion (14). One noninfusion-related side effect seen in the first trial with the anti-CD3 monoclonal antibody otelixizumab was transient Epstein-Barr virus (EBV) reactivation (15). Although the authors concluded that such EBV reactivation was of no apparent clinical concern over the long term, others have asserted that this must be avoided at all costs (16). This writer was Chair of the Data Safety Monitoring Committee (DSMC) for that study, and prior to the study the DSMC had concluded that transient EBV reactivation was possible and would not constitute a reason to halt the study. On the other hand, in an attempt to use a dose that would avoid all side effects, the phase 3 studies with otelixizumab reduced the dose to one-sixteenth of that used in the original trial, which resulted in the study not only avoiding all side effects but also not having beneficial effects (17). This unfortunate dose reduction reminds us that all effective therapies are likely to have some side effects and that if one lowers the dose to eliminate all side effects, the drug may no longer have benefit. Drugs should not be tailored to avoid side effects but be optimized to obtain therapeutic effect, after which the risk-benefit ratio can be assessed.

The phase 3 trials with the anti-CD3 monoclonal antibody teplizumab (5,6) also require comment. The primary outcome measure selected for these trials was the combination of HbA_{1c} $<6.5\%$ and insulin dose <0.5 units/kg/day. This outcome measure was arbitrarily selected without sufficient data to justify its selection. By using a composite outcome, a subject must meet two criteria to be classified, and the selection of a "yes/no" outcome dilutes the effect of two continuous variables: HbA_{1c} and insulin dose. More important, when the conventional outcome measure of C-peptide was assessed, the study results were positive and were especially evident in subjects enrolled in the U.S., in younger subjects (ages 8–17 years), in subjects enrolled within 6 weeks of diagnosis, and in subjects with higher levels of C-peptide at entry (5,6). TrialNet has established a consistent way of measuring C-peptide in response to a mixed-meal challenge and has defined several variables to take into account when assessing C-peptide levels (18).

Anti-CD3 is the most extensively studied immunological approach to T1D. A short course of anti-CD3 (6 to 14 days) early in the course of the disease has the potential to profoundly alter the course of the disease for many years (2,4).

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When used in adequate doses anti-CD3 consistently has been shown to preserve C-peptide (1–7,10). The AbATE trial has demonstrated that in responders the mean preservation of C-peptide continues at baseline levels for 2 years (10). Collectively, the data are persuasive that anti-CD3 needs to move to full-scale phase 3 trials, which are designed to have an adequate dose and an appropriate primary outcome measure (preservation of C-peptide). It would be criminal to not fully study an approach with such compelling results. In addition, subjects with dysglycemia should be encouraged to participate in the ongoing prevention trial using the anti-CD3 monoclonal antibody teplizumab (13).

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