It's Time to Consider Changing the Rules

The Rationale for Rethinking Control Groups in Clinical Trials Aimed at Reversing Type 1 Diabetes

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In some ways, it is difficult to imagine that more than a quarter century has passed since the earliest attempts to reverse type 1 diabetes through immune modulation saw their genesis (1). Sadly, despite the performance of a multitude of clinical trials during this time period ranging from single case studies to large multicenter collaborative efforts, no agent or methodology has been identified as a proven means for reversing this disorder in a setting meaningful to public health care delivery (2). These efforts, like those seeking to prevent the disorder before its symptomatic onset, have not been devoid of providing scientific benefit as many intellectual gains have been realized through their performance (3,4). This would include improvements in assays for immunologic and metabolic biomarkers of disease (e.g., autoantibodies, C-peptide), standardization of tests for metabolic function, the organization of large collaborative networks (e.g., National Institutes of Health [NIH] TrialNet and Immune Tolerance Network), as well as an improved understanding of the natural history for type 1 diabetes; many facets of which have been reported over the years within the pages of *Diabetes*.

To be clear, clinical trials seeking the reversal of type 1 diabetes are tough to perform for reasons large in number and diverse in nature. Often, a therapeutic agent can be difficult to obtain from a pharmaceutical entity (especially if it is in the early stages of development), and even when available, it can be cost prohibitive. Beyond this, costs for laboratory testing, patient care, travel, and mechanistic studies contribute substantially to the bottom line of any clinical trial. Organizational challenges include obtaining regulatory approval at a local (i.e., institutional review board) or national (e.g., U.S. Food and Drug Administration [FDA], European Medicines Agency) level, meeting privacy and compliance issues, recruiting and retaining trial staff, and more. However, once organized, among the most difficult facets—and in some trials, *the* most challenging—is that of patient recruitment. This is certainly the case for clinical trials seeking to reverse type 1 diabetes. Indeed, for many type 1 diabetic patients and their families, the diagnosis of this disorder can carry with it a state of emotional shock that for far too many, handicaps the ability to make clear and wise decisions with confidence. While patients or their family members clearly desire to select a clinical trial offering the best chance for therapeutic benefit, another major factor influencing trial participation involves questions related to the probability of assignment to a control group, usually involving intensive diabetes management alongside of additional clinic visits for studies of disease mechanisms.

Double-blind, placebo-controlled trials have been the mainstay, albeit not the exclusive model, for most clinical trials seeking type 1 diabetes reversal, as they are for a variety of clinical disorders. Without question, this gold standard trial model provides the clearest medical insights as it affords a means for comparing therapeutic efficacy among various study arms within an organized system. Put bluntly, many view uncontrolled trials as providing no benchmark for which to make key posttrial decisions.

However, thanks to the recent efforts of some very well conducted clinical trials at or near the onset of type 1 diabetes and, more importantly, some moderately successful therapeutic outcomes in a few of these trials, we do now have reasonably consistent data on the natural history of the decline in β-cell function, an almost standard use of C-peptide following a mixed-meal stimulation as an outcome marker for β-cell reserve, and some idea of what a successful treatment may look like as soon as 6 months into a trial. It is for these reasons—knowledge gained from past clinical trials, a desire to improve patient recruitment, the need to be more efficient with costs, and more—that it may be time to consider changing the rules and opening for debate two concepts for future clinical trials seeking to reverse type 1 diabetes. Those concepts would be to either develop a universal control group or move toward a system of adaptive trial design (5–7), where a placebo-control group could be "shared" as decisions regarding trial design (including the addition of new agents, assessing biomarkers as outcomes measures, etc.) are subjected to change over time. The development and subsequent adoption of either form of a control group in studies of type 1 diabetes reversal could provide at least five benefits to both health care providers and those with the disease.

First, when obtaining patient consent, knowledge that randomization to a placebo arm is possible provides a deterrent to recruitment. Reducing the chances for assignment to a group that is devoid of experimental treatment should result in improvements with respect to subject enrollment. Second, as noted previously, clinical research is expensive to perform. While certainly variable and dependent on the specific design of a given trial, it is conceivable that substantial reduction in costs would occur were this proposal adopted. From here, one could also

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consider other benefits with the potential confidence-related gains that would occur with the system utilizing either a universal control group or a program of adaptive design. To the former, the benefits of having a universal control group of, for example, 600 patients versus a traditional placebo control arm (in phase II a/b studies of type 1 diabetes reversal) of approximately 6 to 60 patients would appear obvious. It is also plausible that pharmaceutical companies and other funding agencies (both public and private) would see this as a plus given the aforementioned potential for cost reductions and allowances for comparison of agents against what would be a consistent standard. Indeed, for years, the cost-benefit ratio of performing a clinical trial for type 1 diabetes reversal has not been in industry's favor relative to a therapeutic intervention for type 2 diabetes or many other autoimmune disorders. In addition, researchers have, to some extent, been handicapped in interpreting therapeutic efficacy by publication of clinical trial results lacking a standard reporting format (e.g., different ascertainment times, methods for reporting C-peptide data). The adoption of trial designs that redefine control groups with standards amenable to analysis of arms involving a variety of agents could help change this.

There are several organizations and research consortiums to thank for these advances. The NIH- and Juvenile Diabetes Research Foundation–supported TrialNet Consortium put into place some standardized measurements of β-cell function such as C-peptide quantification following the mixed-meal tolerance test. While there may be more informative measures (e.g., the hyperglycemic clamp), the mixed-meal tolerance test has proven itself as both practical and informative by providing consistent observations in the hands of different clinical sites and trials. Industry has also helped by working with private practitioners (i.e., investigators outside of traditional academia) in order to improve the number of available study subjects as well. The impact of industry could, in theory, be enhanced even more were raw data from trials more readily available to the medical community.

Why are these past observations so important? If we look at four major trials that have claimed efficacy (8–11), all showed a benefit in the first three months of follow-up with an increase in C-peptide as compared with start of treatment. For those efficacious trials, as well as similar trials failing to show efficacy (12–15), a very consistent slope of β-cell decline was observed in the control patients as measured by area under the curve or peak C-peptide following a mixed-meal challenge. The first 12–18 months show a linear drop in the control groups that approximates 30–40% of starting β-cell function per 12-month period. Importantly, it is linear from time point zero. Although there was an eventual decline in C-peptide in the efficacious trials, a closer examination of the data suggests that without stabilization of C-peptide concentrations in the first 3 months, there is little likelihood of efficacy at 12 months or longer.

This is good news for all with agents subject to therapeutic testing for type 1 diabetes reversal. It is now conceivable that small phase II trials with short follow-up periods could be an effective way to test whether it is worth pursuing an agent in type 1 diabetes. For example, single treatment arm studies with a mere 3–6 months of follow-up and mixed-meal challenges could provide sufficient information to render the decision to invest in further testing of an agent and expansion to larger trials. What is the basis for this notion? The mean C-peptide loss at 3 months in adolescents and adults in 2 trials, 1,25(OH)2 vitamin D3 and the anti-tumor necrosis factor drug Enbrel (14,15), approximates 7%. With an SD of 10%, less than 20 patients in a treatment arm would be required to detect no loss of C-peptide with 80% power, and 10 patients to detect a rise of the magnitude seen in, for example, the NIH TrialNet Anti-CD20 (Rituxan) trial (11). It is important to note that this model would only be applicable to the pool of patients with the characteristics of those used in recent trials of similar entry characteristics and entry criteria (i.e., onset within 3 months, age range 12–35 years, a minimal amount of residual C-peptide, and type 1 diabetes autoantibody positivity). With respect to children, we are still waiting for reference points. However, these data could soon become available because of the performance of clinical trials in large numbers of children such as the phase III Diamyd vaccine trial.

This is not to say that movement to control groups of a different design than most current efforts would be without their potential limitations. These models of trial design have been criticized for their potential to increase the risk for false assumptions because of type 1 or type 2 errors. Beyond statistical concerns, seemingly subtle differences in diabetes management between investigators performing a novel clinical trial and those practiced in the universal or adaptive control group could be of influence and result in false assumptions. Beyond this, for studies where prospective mechanistic efforts are being performed (e.g., T-cell assays or other immune markers), the limitations afforded by a reduction in the number of placebo control subjects could represent an impediment. Here, one would hope that efforts under current consideration (e.g., the T1DExchange, NIH TrialNet Natural History Study) seeking to obtain patient samples from individuals throughout their natural history of type 1 diabetes may, in part, fill this void. In addition, standards of care for type 1 diabetes may change with time due to the implementation of new therapeutic advances (e.g., continuous glucose monitoring, insulin analogs, insulin pumps). Hence, with time, while the adaptive trial design model may keep up with such changes, a universal control group may need redefining. This would appear especially important for regulatory agencies such as the FDA, where placebo-controlled phase III trials appear, as noted above, as a gold standard.

It is also vital to note that before implementation of any such effort, control arms from a series of clinical trials having largely similar measurements (e.g., those of NIH TrialNet) should be compared by statisticians and experts in trial design to provide assurance that variances across a series of study populations are not of a degree that would render the proposed universal control or adaptive trial design models unsound. Beyond this, thinking optimistically, should one of the agents currently in phase III studies (e.g., Otelixizumab, Diamyd) receive FDA approval as a standard therapy to extend endogenous β-cell function, then the nature of clinical trials in this area may eventually, but not immediately, change. Specifically, for ethical reasons, all studies moving forward may require providing a standard of care arm with one of the approved therapies that is compared with the novel therapy to be evaluated, and thus a true placebo group may not be readily available.

Lastly, from an ethical perspective, one could question the value of continually assigning individuals having type 1 diabetes to the placebo-based arm of trial after trial for

which they would receive no extraordinary clinical benefit beyond that which may be associated with more active care involved in research study participation. Indeed, this latter notion has recently been called into question in a variety of disorders where the clinical sequela and potential for mortality are high or the outcomes of conventional treatment are largely predictable (16).

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