Through the Fog: Recent Clinical Trials to Preserve β-Cell Function in Type 1 Diabetes

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> Dawn portrays shadows and fleeting openings in the heavy fog. First awake, inquisitive eyes attempt to pierce the grayness, searching out a stepping stone secure enough to settle on next. "There it is, a beam showing a path." Anxious dreams of the night begin to fade. He prepares to move forward, cautiously choosing the direction. Adjacent, others stir. Where is the path they saw so clearly only a short while before? Now, only nothingness surrounds them. The imperative that first drove them to start the journey appears less urgent. Stuck in place, feet encased in heavy mud, their despair spreads to others. "Surely this direction is wrong. There must be an easier path," they cry. There is no end to be seen, and we have been traveling many, many years.
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> —A parable by Carla J. Greenbaum

For almost 50 years, type 1 diabetes has been described as an autoimmune disease characterized by the T-cell–mediated destruction of β-cells, which begins long before clinical diagnosis. Clinical trials accepting this premise and aimed at modulating the immune system before or after onset of clinical disease have failed to prevent or cure type 1 diabetes. Nonetheless, clinical trials have provided useful knowledge. Whereas some studies have demonstrated no effect on disease progression, a small number of therapies have transiently delayed the decline of β-cell function in recently diagnosed patients.

In an effort to move toward new therapies for type 1 diabetes, we must continue to seek out the "openings in the heavy fog" of our parable. A review of recently completed clinical trials provides knowledge to guide the rational design of future trials. In that spirit, this Perspectives in Diabetes article focuses on critical lessons learned from: *1*) clinical trials with negative results, *2*) pilot studies, and *3*) clinical trials demonstrating transient effects on β-cell function and suggests directions for future efforts.

LESSONS LEARNED FROM NEGATIVE RESULTS: "SURELY THIS DIRECTION IS WRONG"

Well-powered, randomized, double-masked clinical trials remain the gold standard for documenting efficacy. The creation of clinical trial networks and the concerted efforts of individual investigators and funding agencies have allowed several well-designed studies to be performed in both recently diagnosed and at-risk patients. However, many well-designed trials produce negative results. Such is the case for three studies recently reported in type 1 diabetic patients: *1*) mycophenolate mofetil (MMF) plus daclizumab (DZB), *2*) GAD65-alum, and *3*) intranasal insulin.

Mycophenolate mofetil (a broad immunosuppressant that interferes with purine metabolism), with or without daclizumab (a monoclonal antibody against the α subunit of the interleukin-2 [IL-2] receptor) failed to preserve β-cell function 1 year post therapy as measured by stimulated C-peptide (1). This double-masked, placebo-controlled trial randomized 126 subjects within 3 months of diagnosis. Likewise, the antigen-specific therapy of subcutaneous GAD65-alum (2) failed to alter the natural history of C-peptide when tested in 145 newly diagnosed patients aged 3–45 years. The question remains: should these approaches, studied in large, randomized, intervention trials, be completely abandoned, or should they be pursued in other populations or in conjunction with other therapies?

Neither preplanned subgroup analysis nor post hoc exploration of the impact of dose by body weight showed any evidence of efficacy in the MMF/DZB trial. In addition, no clear signals were detected in studies of changes in immune markers (unpublished observations, Peter A. Gottlieb, Denver, CO). As such, there is no current rationale for continued trials using MMF and DZB.

In the case of GAD65-alum, the answer is less clear. The phase 3 industry-sponsored study also yielded negative results (3), and the first randomized trial involving 10–18-year-old children did not meet its primary end point of improved fasting C-peptide in GAD65-alum–treated subjects; it was only secondary end points of stimulated C-peptide that suggested a possible effect in this population (4). Yet, therapies found ineffective in intervention trials might be effective for prevention trials if they were biologically plausible and safe. It had been previously suggested that antigen-based therapy might be more effective if provided early in the disease process or in combination given that the T-cell repertoire against β-cell antigens expands as the disease progresses (5,6). In favor of antigen effects in prevention therapies, a post hoc analysis of oral antigen (insulin) administration in at-risk individuals demonstrated a 4-year delay in the onset of disease in subjects with higher titers of insulin autoantibodies (7) and is now the basis for a large confirmatory randomized trial. Given the difficulties in conducting fully powered prevention trials, additional data are needed before committing to prevention therapy approaches with GAD65-alum. With this aim in mind, the Type 1 Diabetes TrialNet GAD65-alum study group is examining GAD65-specific immune responses through assays, such as tetramers, ELISPOT, flow markers, and transcript profiling. In the absence of overall clinical efficacy, these markers may nonetheless provide information about whether the doses used had biologic effects or may enable identification of subjects more or less likely to have an immune response. If no such signs can be identified,

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GAD65-alum approaches should be abandoned or considered only in combination with other agents. Such combination therapy approaches should first be tested in pilot studies primarily designed to produce supportive data for fully powered trials.

A third trial that recently provided negative results was the Diabetes Prediction and Prevention (DIPP) study from Finland (8). High-risk children (264 of 100,000 screened) were randomized to receive nasal insulin or placebo to test the hypothesis that mucosal antigen presentation would induce tolerance. Although this approach proved both feasible and safe, no preventative effect was seen. Should this approach be abandoned too? After careful scrutiny of the DIPP study, investigators of the similarly designed Intranasal Insulin Trial II (9) decided to continue their study testing nasal insulin in at risk subjects. Their rationale was that antigen therapies depend critically upon dose and frequency, characteristics that are different when comparing Intranasal Insulin Trial II and DIPP. Moreover, mechanistic data from a separate trial of nasal insulin demonstrated reduced insulin antibody levels with therapy and a reduced interferon-γ ELISPOT response to recombinant proinsulin with treatment, supporting the concept that immune deviation can occur with antigen therapy (10). Conducting fully powered, multiarm trials using different doses and frequencies is the ideal approach to develop antigen-based prevention therapy. The enormous costs, in both human and economic capital, required to identify, enroll, and follow at-risk subjects have made such approaches largely untenable. We may be forced, for practical if not scientific reasons, to use smaller pilot studies with mechanistic end points and focused on dose escalation and timing of therapy to enhance the probability that the agents chosen for the definitive trials will provide the desired clinical outcome.

LESSONS LEARNED FROM PILOT STUDIES: "SEARCHING OUT A STEPPING STONE"

More than 30 human clinical new-onset trials were reported before 2001, with the vast majority reporting positive results (11). Many studies were too small or had weaknesses in study design, making interpretation difficult. Three recent reports highlight the potential value of small studies in understanding mechanisms and assessing biomarkers as well as the need for caution in interpreting metabolic changes in these trials.

The first was a phase 1 study combining IL-2 and rapamycin with the aim to augment T-regulatory cell and inhibit T-effector cell function. The approach was rationally designed with supportive NOD mouse studies. Adults up to 4 years from diagnosis who had residual C-peptide secretion received 1 month of IL-2 and 3 months of rapamycin (12). Three months after enrollment, all subjects had a marked and unexpected fall in C-peptide compared with their prestudy values. The fall in C-peptide at 3 months reflected transient treatment-induced β-cell dysfunction and not β-cell death, as an increase in C-peptide was observed in later visits. The consistent C-peptide results in all patients led to the conclusion that the combination of IL-2 and rapamycin in the route, frequency, and doses given was not acceptable in this population. Additional studies demonstrated an increase in T-regulatory cells with therapy, sustained resolution of the impaired responsiveness of these cells to IL-2, and an increase in the number of natural killer cells and eosinophils. The question remains whether other dosing regimens could be devised that would prevent induction of cells or cellular products that injure the β-cell while preserving the desired effects seen in T-regulatory cells. Although we do not yet understand the mechanism by which these agents may have led to transient β-cell dysfunction, this pilot study has been informative. We learned that this combination in the doses given is unacceptable. The study data remind us that looking only for mechanisms or biomarkers that we expect to see (e.g., measurement of T-regulatory cells) may give an insufficient picture of the effects of therapy. Nonetheless, this small study is an important stepping stone toward further therapies aimed at the IL-2 pathway.

A second phase 1, masked, placebo–controlled pilot study used a crossover design to test a plasmid vector to deliver proinsulin with the aim of efficiently triggering dendritic cells to alter the immune response (13). The abstract suggested that treatment with this vector was associated with β-cell preservation. The differences in time from diagnosis of subjects who did and did not receive drug and the unusually rapid rate of fall of C-peptide in the adults in the placebo group points to the inadvisability of suggesting efficacy in this small pilot study. The reassuring safety data from this trial should have only led to a discussion about whether to conduct additional studies to further explore dose or mechanism or whether to pursue a phase 2 study powered to evaluate C-peptide.

A third pilot study involving autologous nonmyeloablative hematopoietic stem cell therapy is controversial (14,15). Previous studies of this approach in other autoimmune diseases demonstrated significant morbidity and mortality with variable benefits (16). Twenty of 23 subjects discontinued insulin therapy post stem cell therapy, with many remaining off insulin for 1 to 2 years. A subgroup of subjects demonstrated increased C-peptide 1 and 2 years post intervention. The long-term follow-up of these aggressively treated patients will be important to fully assess overall risk and benefits. Although the open-label design and high-risk therapy require cautious interpretation, the results challenge us to learn about mechanisms involved in this approach. Is the effect from the stem cells given or the induction therapy? Studies aimed at deconstructing this combination approach are underway and should allow us to rationally design future studies with a reduced side effect profile while preserving efficacy.

LESSONS LEARNED FROM PHASE 2 STUDIES DEMONSTRATING TRANSIENT PRESERVATION OF β-CELL FUNCTION: "THERE IT IS, A BEAM SHOWING A PATH"

Three therapies with distinct immunologic mechanisms of action have been shown to preserve β-cell function (decreased rate of fall of C-peptide) in some, but not all trials: anti-CD3 (oxelizumab and teplizumab), anti-CD20 (rituximab), and costimulation blockade (abatacept) (Table 1).

In studies utilizing the humanized anti-CD3 molecule oxelizumab, 80 subjects were randomized to receiving oxelizumab or placebo (17). Anti-CD3 therapy is effective at reversing hyperglycemia in animal models, and several mechanisms have been suggested to explain its effects (18–21). Drug-treated subjects had a slight increase in C-peptide from baseline at 6 months, whereas levels fell in placebo-treated subjects. Drug-treated subjects also used less insulin while maintaining good glycemic control. Follow-up demonstrated a delay in the rise in insulin requirements among a subgroup of treated individuals for 4 years post therapy (22). Short-term side effects in the original study, including cytokine storm and apparent reactivation of Epstein-Barr virus, led to

TABLE 1
Key measures in selected trials of recently diagnosed patients

Study	Reported end points	Age (years)	C-peptide entry criteria	Time from diagnosis to initial test	*N*		Placebo (control)[1]			Treatment[1]			Treatment effect	
					Treatment	Placebo	Start value	1-year value	Percent change in first year	Start value	1-year value	Percent change in first year	Absolute difference at 1 year[2]	Relative difference at 1 year[3]
A, hOKT3γ1 (Ala-Ala), teplizumab (25)	Change in AUC C-peptide: $P < 0.001$	7–30	Not specified	<6 weeks of diagnosis[4]	21	21 (control)	~0.48	~0.27	~−44.8	~0.49	~0.49	~−0.8	~0.22	~1.83
B, ChAglyCD3, oxelizumab (17)	Change in AUC C-peptide: $P = 0.01$	12–39	>0.2 pmol	~23 days (median)	40	40	~0.95	~0.72	~−24.2	~0.85	~0.90	~5.9	~0.18	~1.25
C, rituximab (29)	AUC C-peptide at 1 year: $P = 0.03$	8–45	>0.2 pmol	~82 days (mean)	52	29	0.74	0.47	−36.5	0.75	0.56	−25.3	0.09	1.19
D, abatacept (30)	AUC C-peptide at 2 years: $P = 0.0029$	6–45	>0.2 pmol	<80 days (mean)[5]	77	35	0.75	~0.45	~−40.0	0.74	~0.57	~−23.0	~0.12	~1.27
E, teplizumab (26)	Primary outcome: insulin use <0.5 units/kg and HbA_{1c} <6.5%, P = NS; secondary outcome: change in AUC C-peptide: P = NS	8–35	Detectable	~8.4 weeks (mean)	207	98	0.65	0.56	−13.8	0.65	0.59	−9.2	0.03	1.05

[1]β-Cell function tests: Study A, mean C-peptide area under the curve (AUC) values from 4-h mixed-meal tolerance test (MMTT) read from Fig. 2 in published results and therefore may lack precision, as indicated by ~; value on figure divided by 240 to obtain pmol/ml/min; Study B, mean C-peptide AUC values from glucose and glucagon stimulation as read from Fig. 1 in published results and therefore may lack precision, as indicated by ~; Study C, mean C-peptide AUC values from 2-h MMTT as reported; Study D: Mean C-peptide AUC values from 2-h MMTT. Initial values as reported. One-year values read from Fig. 3 in published results and therefore may lack precision, as indicated by ~; and Study E, mean C-peptide AUC values from 4-h MMTT. Initial values as reported in Table 1 in the article by Sherry et al. (26). One-year values were calculated by subtracting the change from baseline for each group as reported in Table 2 in the article by Sherry et al. (26). [2]Absolute difference: 1-year value treatment group minus 1-year value placebo (control) group. [3]Relative difference: 1-year value treatment group divided by 1-year value placebo (control) group. [4]Entry criteria: mean time from diagnosis of enrolled subjects not apparent from publication. [5]Time to first infusion reported as 88 and 83 days for treatment and placebo groups, respectively; initial MMTT conducted at screening a minimum of 2 weeks and a maximum of 4 weeks prior.

subsequent small studies aimed at determining a dose without side effects. These data led to a placebo-controlled phase 3 trial incorporating a dose ~15-fold lower than that used in the original study (23); unfortunately, no effect on stimulated C-peptide was detected. Although not proven, it is reasonable to assume that the negative results may have been from selecting the lower dose for trial. This trial highlights the conundrum facing immunotherapeutics in type 1 diabetes similar to that seen in the equipoise decisions surrounding nonmyeloablative pilot studies; high-dose/high-risk therapies may have untoward effects, whereas too low-dose/low-risk therapies may simply be ineffective.

A second humanized anti-CD3 molecule (teplizumab) was studied in an open-label trial of 24 subjects; 9 of 12 drug-treated subjects maintained C-peptide as compared with 2 of 12 in the observation group (24). Subsequent articles have reported the results of this cohort along with an additional 18 subjects with similar outcomes (25). As in the oxelizumab trial, the effects of teplizumab appeared early and then waned as the rates of fall in C-peptide concentration of treated and untreated subjects were parallel 3–6 months post therapy. A phase 3 trial was then undertaken in which subjects received two courses of teplizumab 6 months apart (26). As a result of prespecified clinical parameters, 14% of subjects were unable to complete these courses. The primary outcome selected for the phase 3 trial was not C-peptide, but rather a combination of insulin dose and HbA_{1c} which may, at first glance, seem more directly clinically relevant and therefore appealing than C-peptide. However, this was likely a poor choice for at least two reasons: *1*) C-peptide is the most direct measure of β-cell function, and *2*) glycemic control and insulin requirements are highly dependent on patient behaviors that may not fully reflect β-cell function. In any case, there was no significant effect of drug therapy on this clinical primary outcome or the prespecified secondary outcome of C-peptide.

Another important trial using teplizumab was recently presented (27). In this non–placebo-controlled randomized study, 81 subjects received 14 days of drug in two courses a year apart. C-peptide was significantly higher in the treated as compared with observational subjects at 1 and 2 years. Repeat dosing did not appear to have additional beneficial effects. Although the results of phase 3 trials with anti-CD3 agents are disappointing, they should not be particularly surprising. Development of new pharmaceuticals is a high-risk endeavor even after initial positive results in phase 2 trials that include highly selected subjects. Only 11% of all new drugs progress from first-in-man to therapeutic use, with >50% failing at phase 3 due to lack of efficacy (28). It is clear that more work is needed to better understand the timing, dosing, and population for anti-CD3 agents before clinical use.

A second approach that has demonstrated transient preservation of β-cell function uses the anti–B-cell drug rituximab. In a placebo-controlled, double-masked, phase 2 trial with 81 subjects, those receiving rituximab had an increased C-peptide at 1 year compared with placebo. In addition, there was less insulin use and better glycemic control among rituximab recipients (29). However, as with the anti-CD3 therapies, the effect on C-peptide was early, primarily within the first 6 months, after which the slopes between drug- and placebo-treated groups were parallel. Although compelling, results from even well-designed phase 2 studies are insufficient to recommend any therapy for clinical use.

A third agent demonstrating promise is the anti-costimulation drug abatecept (cytotoxic T-cell–associated antigen 4-immunoglobulin). In a similar phase 2 trial design, 103 subjects were randomized to monthly infusions of drug for 2 years or placebo (30). After 2 years of this well-tolerated therapy, drug-treated subjects had significantly greater C-peptide levels than those receiving placebo; yet once again, the effect appeared early only to wane, with treatment resulting in a 9-month delay in the eventual parallel decline in C-peptide. Long-term data on this cohort, likely available within a year, will be critical to informing future clinical trials or eventual clinical use.

What, then, are the lessons learned from these trials demonstrating transient effect on β-cell function? Among the three interventions with positive outcomes, all had very similar results; specifically, all delayed the fall in C-peptide, but failed to attenuate the eventual rate of decline (Fig. 1). Repeat dosing of anti-CD3 or with continued therapy with abatecept failed to affect the natural course of disease. The similarity in C-peptide response despite the considerable differences in the three approaches may be the most important collective observation from these trials and might be telling us something fundamental about our approach to the disease or the disease process itself. In some cases, we may be forced to accept that therapies will remain ineffective when applied to patients in whom the disease process has already progressed. Alternatively, perhaps what we perceive as pure autoimmune disease more accurately has two components, a chronic autoreactive T-cell–driven path overlaid with acute inflammation leading to β-cell dysfunction, as well described in the IL-1β model (31). The data from a small study using anti-tumor necrosis factor supports the notion that local inflammation is one component of type 1 diabetes (32), and data from ongoing trials using other anti-inflammatory agents such as anti–IL-1 (33) and α1-antitrypsin (34) therapies will likely be instructive.

"WHERE IS THE PATH THEY SAW SO CLEARLY ONLY A SHORT WHILE BEFORE?"

To move forward, we must continue to incorporate new information being gathered about the natural history of disease. The Eisenbarth model published in the 1980s pointing to the predictive role of autoantibodies with progressive destruction of β-cells over time is supported by decades of clinical research and has proved to be useful in the design and conduct of clinical trials to date (35). As satisfying as this model has been, it provides no information about disease mechanisms or heterogeneity before or after clinical onset of disease that may help in selection of new therapies or trial designs. We need to better understand what is happening to the β-cell, particularly at initiation of disease and in the peridiagnosis period, considering new observations such as the vitiligo-like pathology of human insulitis (36) and metabolomic signals preceding the appearance of autoantibodies (37). We know that C-peptide production is stable for years before diagnosis, only to drop precipitously at the time of the diabetic oral glucose tolerance test (38). Yet, data comparing what happens to C-peptide across the diagnostic period is limited and confounded by the fact that the function of the β-cell depends upon the antecedent metabolic state. Although impractical in the context of clinical trials, interrogating the β-cell through assessments such as maximal insulin secretion in a limited number of subjects may allow for better understanding of β-cell status and the effects of therapy.

We also need to reconsider the populations in which we test therapies. Decades of study now allow identification of subjects with 25–50, >50, and ~90% risk over 5 years (39–46).

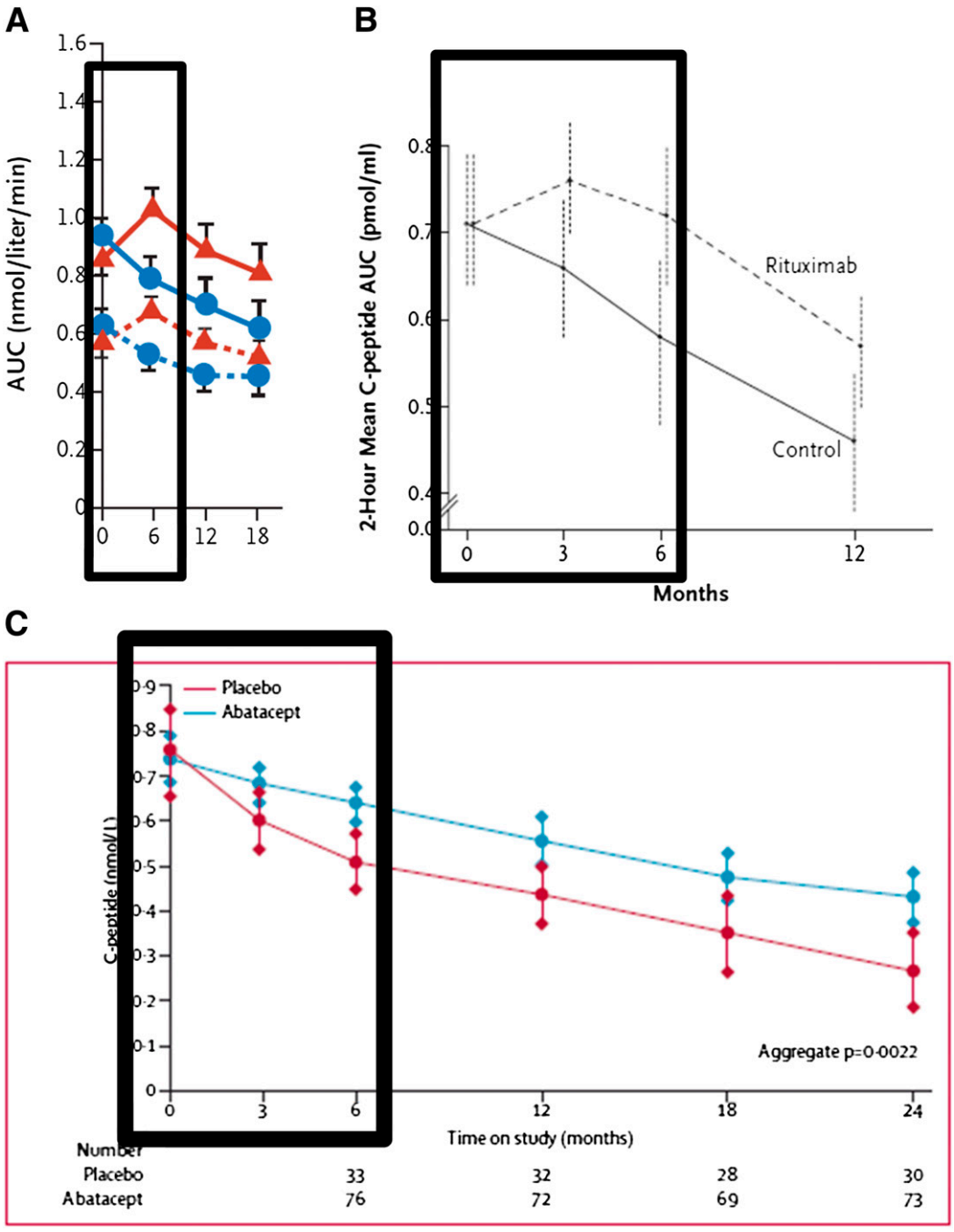

FIG. 1. Effects of therapy to preserve β-cell function appear early. Solid black box is shown in each panel to emphasize time period of therapeutic effect. *A*: Circles represent the placebo group, and triangles represent the ChAglyCD3 group. Dashed lines show the glucose clamp–induced C-peptide release before glucagon injection and solid lines show after glucagon injection. Reprinted with permission; copyright Massachusetts Medical Society, 2005 (17). *B*: Area under the curve (AUC) C-peptide from 2-h mixed-meal tolerance test in placebo (solid line) and rituximab-treated (dashed line) subjects. The 95% confidence limits are shown at each time point within each group. Reprinted with permission; copyright Massachusetts Medical Society, 2009 (29). *C*: Population mean of stimulated C-peptide 2-h AUC mean over time for each treatment group (placebo, red; abatacept, blue). The estimates are from the ANCOVA model adjusting for age, sex, baseline value of C-peptide, and treatment assignment. Error bars show 95% CIs. Reprinted with permission from *The Lancet* (30).

Critically, because altering the course of β-cell function in these groups would have a clear-cut clinical benefit (i.e., delay onset of clinical disease), the case for primary or secondary prevention trials (e.g., before or after the development of autoantibodies) is compelling. Moreover, primary prevention may be easier to achieve than stopping progression after the disease process has begun. However, identification of these populations requires testing thousands of subjects, limiting the ability to rapidly enroll and evaluate different therapies and different doses in fully powered trials. Standard screening, incorporated into routine office visits, although rife with regulatory, ethical, and logistical issues, could improve this picture. In the absence of such a radical change in approach, priority should be given for small, proof-of-concept or mechanistic studies in the at-risk populations. Away from the confounding issues of insulin administration and glycemic control and the uncertain clinical benefit of transient

C-peptide preservation, small studies in this population are likely to be informative.

In contrast to studies in at-risk individuals or those recently diagnosed, there are pragmatic advantages to testing therapies in those outside the first few months from diagnosis, as many more people would be eligible for trial; however, there are several disadvantages as well. First, previous studies have all suggested more of a benefit of therapy in those closer to disease onset. As a result, there is a risk that a new therapy may have no effect in this population when it might have had an effect if tested earlier. Second, with limited information about the decline in C-peptide ≥2 years post diagnosis, it is difficult to design a study to evaluate effects of therapy on β-cell function in this group. With current knowledge, the disadvantages outweigh the advantages for conducting studies in this population.

It has become almost de rigueur in review or opinion pieces to call for combination therapies. Certainly, cancer therapies have advanced using this approach, and this is commonly used in other autoimmune diseases. However, depending on the combinations chosen, there may be substantial regulatory and logistic hurdles with this concept, including the necessity for extensive preclinical toxicity studies. In truth, as proven by the similar clinical results obtained with drugs presumably affecting different aspects of the immune response, we know little about how therapies actually are effecting β-cells; thus, combining two or more systemically active immunotherapeutic approaches may result in unexpected outcomes. Combination therapies seeking to find synergy can and should be developed but must be designed rationally with a better understanding of the proposed mechanisms involved.

What have we learned from the approaches during the past decade or so to enable greater success in the future? We must move beyond the low bar of effectiveness in the NOD mouse to in vitro studies with human samples and in vivo studies focused on mechanistic outcomes (Fig. 2). These efforts will help dissect out the pathophysiology that must underlie the clinical heterogeneity seen. An important offshoot of the recent clinical trials is a wealth of blood samples available for further study. For example, the standard test of a new biomarker assay is comparison between groups (e.g., treated versus not; diabetes versus not). However, within each group, there is always a range of values and understanding the implications of these variations is likely to lead to important observations about disease heterogeneity.

Testing of samples from observational studies could direct ideas for therapies to test; however, this is insufficient. As endocrinologists, we should also take a page from our history. By perturbing the system, much can be learned. Small studies, properly termed clinical research instead of clinical trials in which a drug is used for the purpose of investigating the immune response or β-cell activity, should be the key link between preclinical experiments and classic phase 1 clinical trials. With the understanding that any one

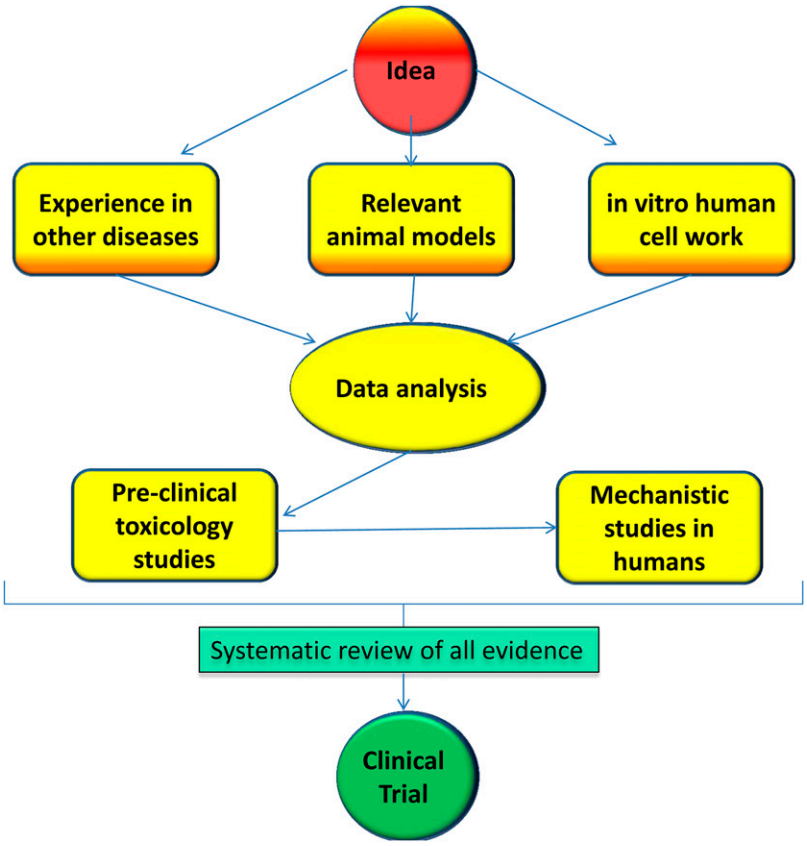

FIG. 2. Deciding which therapies to bring to phase 2 clinical trial. To enhance confidence that a phase 2 clinical trial will prove efficacious, we must guard against evidential conservatism which is the tendency to base clinical inferences on narrow classes of evidence (47). Decisions about which therapy to bring to clinical trial have often been made by evaluation of results in a single animal model, another autoimmune disease, or by data collected with the aim to demonstrate the expected effect. In other words, in our enthusiasm to bring new discoveries to trial, we heavily weigh evidence that supports the new ideas. Before launching a full-scale clinical trial, dispassionate and systemic collection and review of the totality of data including in vitro studies with human samples and in vivo proof of mechanism clinical studies are needed.

experiment will not provide definitive answers, preliminary safety, clinical, and mechanistic data from pilot studies are useful before making the jump to larger clinical trials. For example, although safety concerns or negative clinical effects make the decision to forgo further clinical trials straightforward, the decision is more nuanced in the absence of any such data. Mechanistic data, whether demonstrating that the proposed mechanism of action from preclinical studies is relevant in humans or that unexpected off-target changes are occurring, can lend weight to a decision about whether or not to move forward to clinical trial. As discussed by Kimmelman and London (47), making go/no-go decisions to move to the next stage in clinical trial development are strongly affected by the desire to succeed. Through systematic and nonarbitrary review of all relevant data, we can guard against evidential conservatism, defined as the tendency to base clinical inferences on narrow classes of evidence.

To move therapies toward eventual clinical use, a parallel research track is needed to further define the potential clinical benefits of C-peptide preservation. In other autoimmune diseases, currently approved therapies have effect sizes in the range found in the type 1 diabetes clinical trials described above. The obvious issue is that reducing an immune response around β-cells cannot be compared with the reduction in joint pain that would be seen with effective immunomodulatory treatment of rheumatoid arthritis. As stated above, preventing or delaying onset of clinical disease is an obvious benefit. However, although studies support the notion that endogenous β-cell function in those with disease is associated with important clinical outcomes (48), the degree and duration of endogenous C-peptide likely to provide a minimum or maximum benefit is unknown. Thus, parallel with clinical trials to test therapeutic effects on β-cell function, studies evaluating the relationship of C-peptide secretion not only with clinically important straightforward variables such as hypoglycemia and complications, but also with as yet vaguely defined parameters such as whether the clinical course is easier to manage in those with residual β-cell function are needed.

Despite decades of effort, the goal of preventing or halting β-cell destruction has not yet been achieved, and the pathway to achieve this goal remains elusive. To see our way through the fog, we must increase our understanding of the heterogeneous natural history of type 1 diabetes, focus efforts on preventing clinical onset of disease, perform proof-of-concept pilot studies prior to embarking on large clinical trials, and more fully explore the relationship of residual insulin secretion and clinical outcomes.

> Dawn portrays shadows and fleeting openings in the heavy fog. “Listen,” he implores them. “Hear the voices depending on us.”

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