Recent Lessons Learned From Prevention and Recent-Onset Type 1 Diabetes Immunotherapy Trials

Teodora P. Staeva,[1] Lucienne Chatenoud,[2] Richard Insel,[1] and Mark A. Atkinson[3]

Type 1 diabetes (T1D) results from the immune system's misguided attack on insulin-producing pancreatic β-cells, leading to lifelong insulin replacement therapy as well as to the risk for developing disease-associated complications (1–3). Over the past 2–3 decades, the field of clinical research in T1D has seen tremendous growth, including evaluation of a variety of promising immunotherapy approaches for the prevention or reversal of the disorder (4–6). In just the past 2 years, data from >10 trials have been reported, some revealing promising phase II results. However, phase III trials have failed to demonstrate efficacy. In light of these results, an anxiety-provoked question has arisen: Where does the field go from here? To this end, this article presents and elaborates on key emerging questions and recommendations for future immunotherapy trials in T1D. If implemented successfully, such strategies could accelerate the development of therapies with tangible clinical benefit in T1D because they perhaps more appropriately address the complex nature of the disease.

WHY IS IT IMPORTANT TO EXAMINE THE HISTORY OF IMMUNE INTERVENTION IN T1D?

Nearly 30 years after the first immunotherapy clinical trials in type 1 diabetes (T1D), progress has been realized. This progress includes advancements in scientific knowledge (e.g., immune markers, metabolic testing, pathogenesis), the breadth of agents under investigation (Fig. 1), and how clinical trials are increasingly performed as part of major collaborative networks with uniform protocols often bolstered with mechanistic assays. However, shortcomings remain in demonstrating a degree of therapeutic efficacy for recent-onset T1D immunotherapies that is sufficiently robust in terms of risk/benefit to satisfy the requirements for drug registration and approval by regulatory agencies (i.e., Food and Drug Administration, European Medicines Agency). In 2011 and early 2012 after a number of phase I and II recent-onset clinical trials, a series of phase IIB and III recent-onset T1D trials reported their outcomes (7–10). In advance of these reports, at least one editorial expressed concern about the impact negative trial findings

would have on the T1D research community (e.g., pharmaceutical companies, researchers, health-care providers, patients and their families) (11). True to form, a degree of anxiety has arisen in the field, sparked largely by the disclosure that each of three recent T1D phase III trials (i.e., two with anti-CD3 and one with GAD-alum) failed to meet their primary end point. Indeed, only a DiaPep277 (Andromeda Biotech) phase III recent-onset T1D trial in subjects 16–45 years of age avoided this trend (12,13).

With these outcomes, some have considered it timely to question whether the notion of preserving residual β-cell function with immunotherapies in recent-onset T1D is too difficult a goal to achieve. We would, with a strong sense of conviction, suggest that the appropriate answer to this question is no. At the same time, we portend it vital to reexamine both the design and the outcomes of these recent phase II and III trials for the purpose of understanding the limitations of those studies, identifying critical knowledge gaps, and planning more-effective strategies to accelerate progress and enhance the potential for success of future trials.

CURRENT STATE OF AFFAIRS: CHALLENGES AND OPPORTUNITIES

Immune intervention in the new-onset setting can delay T1D progression, at least temporarily. Proof of concept that immune intervention can effectively delay new-onset T1D progression was demonstrated in the 1980s in trials using cyclosporine. When administered within 2 months after initiation of insulin therapy, cyclosporine induced remission of the disease with insulin independence (Fig. 2) for the duration of treatment (14–17). However, drug toxicity, particularly nephrotoxicity, represented a noteworthy adverse event that limited enthusiasm for this form of therapy. An additional limitation was that the therapeutic effect of cyclosporine vanished with cessation of treatment, as has also been observed in other clinical situations (e.g., autoimmune diseases, transplantation) where the drug was used (18). In other words, cyclosporine did not induce immune tolerance or immunoregulation but merely a state of immunosuppression, implying that cyclosporine would need to be administered indefinitely to maintain its therapeutic effect, an approach fraught with potential infectious and tumorigenic risks. Other immunosuppressive agents have also demonstrated therapeutic efficacy in settings of recent-onset T1D, but even in the face of continued use, these failed to show durable effects. For example, the fusion protein CTLA4-Ig (abatacept) preserved stimulated C-peptide for only ~9.5 months despite continuous administration for 2 years (8,19). These results imply that immunosuppression with abatacept is insufficient to completely control the autoimmune destruction of β-cells, suggesting that more-robust immunosuppression or possibly combination therapy is
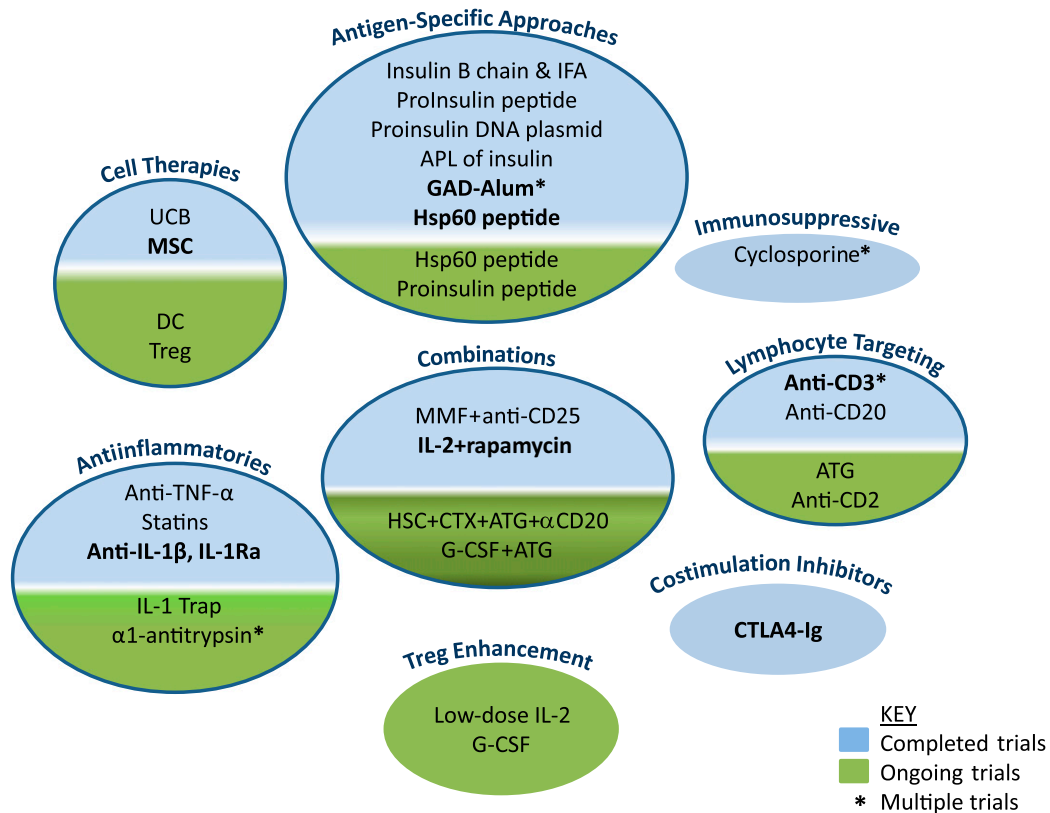
FIG. 1. Immunotherapies clinically tested or under testing in recent-onset T1D. Interventions appearing in bold represent therapies reported in trial results during the past 20 months. APL, altered peptide ligand; CTX, Cyclophosphamide (Cytoxan); HSC, hematopoietic stem cell; Hsp, heat shock protein; IFA, incomplete Freund's adjuvant; IL-1Ra, interleukin-1 receptor antagonist; MMF, mycophenolate mofetil; MSC, mesenchymal stem cell; UCB, umbilical cord blood.

required. An additional possibility is that in some subjects, there may be a finite window of opportunity after diagnosis to preserve residual β-cell function, with the eventual loss over time of dysfunctional β-cells even with ongoing immunosuppression. Supporting this concept is the observation that the initial administration of anti-CD3 immunotherapy >8 months after diagnosis proved less effective than treatment in the recent-onset period in preserving β-cell function (20).

Even aggressive immunosuppression combined with rebooting of the immune system has shown only temporary effects. A trial of autologous hematopoietic stem cell

FIG. 2. Effect of cyclosporine treatment on T1D remission rates, as reported by the Cyclosporine Diabetes French Study (15). CsA, cyclosporin A.

transplantation combined with high-dose immunosuppression (i.e., Cytoxan [Bristol-Myers Squibb Company] and Thymoglobulin [Genzyme Corporation, a Sanofi Company]) was able to induce insulin independence in a majority of patients treated at disease onset (21). However, the effects of this rather invasive treatment waned over time, with loss of insulin independence in most subjects over a 5-year period. This relapse of autoimmunity with time with these approaches may be arising from autoimmune memory lymphocytes that persist and prove resistant to therapy.

Induction of stable β-cell–specific immune tolerance would be ideal. The best solution to overcome the aforementioned limitation of immunosuppression is to induce immune tolerance, which although subject to many individual definitions, could operationally be noted as the inhibition of disease pathogenic responses with control of autoimmunity in the absence of chronic immunosuppression. Although many attempts have been directed at such a notion, two approaches have garnered the most attention.

Autoantigen-based approaches for T1D. Based on a strategy developed in other autoimmune diseases as well as in nonobese diabetic (NOD) mice, one approach to induce immune tolerance involves the use of β-cell autoantigens. The notion of antigen-specific immunotherapy raises the issue of what is the best autoantigen to use, which is confounded in T1D by the existence of several candidate β-cell autoantigens (e.g., insulin, GAD, ZnT8, proinsulin). Fortunately, experimental studies have shown that in contrast to deletional or anergic immune tolerance, the induction of regulatory cells to one autoantigen can
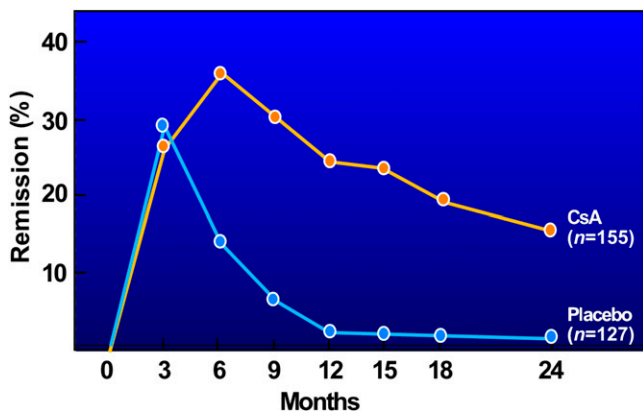
extend tolerance to other autoantigens through an immunological phenomenon described as bystander suppression (22–26). This is a central issue because by inference, it suggests that the selection of the autoantigen may not be limiting.

Perhaps more daunting, however, is the observation in NOD mice that treatment with β-cell autoantigens work with highest efficiency when administered earlier in the course of the disease, long before the onset of hyperglycemia (i.e., at a very early stage of the immune disease) (24–27). This may reflect the fact that with several vaccines, multiple doses of autoantigen are required for efficacy or, alternatively, that with time, epitope spread outpaces the ability of antigen-specific immunotherapy to control the autoimmune response. Thus, with translational inference, it may not prove feasible to preserve β-cell function in recent-onset human T1D with autoantigen therapy alone. Such a notion may partly explain the negative results observed with GAD-alum (Diamyd) recent-onset T1D trials (7,10).

Future trials that use this approach should be developed thoughtfully, using immunological markers perhaps as a parallel end point, with special attention given to carefully defining the optimal antigen dose in humans. Additional challenges, however, remain, including the wide heterogeneity of T1D, the limitation of lymphocyte analysis from peripheral blood, and the unclear relationship between immune and metabolic changes during the course of disease development. Despite or perhaps because of these challenges, T1D immunotherapy trials may need to be designed differently to focus on relatively small sample sizes with short (e.g., 6-month) mechanistic outcomes. Such studies could aid in dose optimization, allow for the development of reasonable predictions for the outcomes of larger trials, and provide insights into the mechanism of action of the therapy. A list of potential mechanistic assessment candidates would include but not be limited to cytokine release (interleukin [IL]-1, IL-2, IL-13, IL-17, IL-23, IL-35), T-cell receptor isotype usage and downregulation on autoreactive T cells; costimulatory molecule expression (PD-1, PD-L1, CD70, CD40L), T- and B-cell maturation and phenotype, dendritic cell (DC) maturation and cytokine (IL-10) secretion, chemokine and chemokine receptor expression, and proteomics of many T-cell receptor-dependent signaling pathways of activation and apoptosis.

Improved efficacy of human autoantigen-specific vaccines may also be observed if used in either the primary or the secondary prevention setting (Table 1) where the timing may not prove as critical and the autoimmune response not as extensively expanded. Examples of efforts testing such a notion include the use of oral insulin in patients with antiinsulin autoantibodies (National Institutes of Health TrialNet Oral Insulin Study), intranasal insulin in at-risk individuals (INIT II [Intranasal Insulin Trial]), and oral insulin vaccination in children with very high familial and genetic risk (Pre-POINT [Primary Oral/Intranasal Insulin Trial]) (5,28). Finally, another possibility would involve the use of autoantigens as a valuable component of combination therapies, a strategy for which there is accumulating experimental support (29).

Immunoregulatory-based approaches to T1D therapy. The second major or overall approach to inducing immune tolerance involves the use of agents that interfere with T-cell signaling and have the ability to delete and anergize deleterious effector cells as well as induce dominant suppressive regulatory cells. These include anti-CD3 monoclonal antibodies (teplizumab and otelixizumab) (30–33). These biological agents induce sustained remission of diabetes for indefinite periods in NOD mice, whereas their immunosuppressive effects only last a few weeks after treatment (34–37).

Data from phase II recent-onset T1D trials with anti-CD3 have been conclusive with regard to their therapeutic efficacy and benefit (20,30–33). Taken collectively, residual C-peptide was preserved compared with the placebo control group for up to 2–4 years. Based on the phase II trials' results, phase III trials with teplizumab and otelixizumab were conducted, but neither met their primary end point (9,38). Of note, both phase III trials had alterations in their trial design from that of the phase II trials, which likely sheds light on their failure to meet trial end points (Table 2). In the case of otelixizumab, the antibody dose for the phase III trial was reduced to one sixteenth the dose administered in the phase II study, with a goal of maintaining efficacy and decreasing side effects observed in phase II trials of limited cytokine release (30–32) and transient reactivation of Epstein-Barr virus in some subjects (32,39). The dose used was based on presumed biomarkers of efficacy, which had never been established conclusively in the phase II trials. In the phase III trial of teplizumab, the dose was adequate, but the end point chosen, one based on a composite HbA_{1c} level (6.5%) and insulin dose (<0.5 U/kg/day), not only was potentially unrealistic, but also would have given a negative interpretation of the successful phase II data. In fact, data from the phase III teplizumab trial, when subject to a post hoc analysis using conventional end points (i.e., the release of C-peptide following glucose stimulation) showed

TABLE 1
Agents currently under clinical testing for prevention of T1D

Agent	Mechanism or target	Phase	Principal investigator/network
Primary prevention trials			
Oral insulin (Pre-POINT)	Oral antigen-specific tolerance	I/II	Bonifacio/JDRF/BMBF Germany
Hydrolized cow's milk (TRIGR)	Immune mimicry	II	Akerblom/TRIGR Study Group
Omega-3 fatty acids (NIP)	Antiinflammatory	Pilot	Chase/TrialNet
Secondary prevention trials			
Intranasal insulin (INIT II)	Mucosal antigen-specific tolerance	II	Harrison/DVDC
Oral insulin	Oral antigen-specific tolerance	III	Krischer/TrialNet
GAD-alum (Diamyd)	Antigen-specific tolerance	I	Larsson/Diamyd/JDRF
Anti-CD3 (teplizumab)	T-cell modulation	II	Herold/TrialNet

BMBF, Federal Ministry of Education and Research; DVDC, Diabetes Vaccine Development Centre; NIP, Nutritional Intervention to Prevent Type 1 Diabetes; TRIGR, Trial to Reduce IDDM in the Genetically at Risk.

TABLE 2
Recent-onset T1D immunotherapy trials reporting results during the past 18 months

Therapy	Phase	No. patients enrolled	Outcomes	Potential explanation/interpretation of results	Next steps	Ref.
Teplizumab	III	516	Did not meet primary end point	Inadequate end point; post hoc analysis using a C-peptide end point demonstrated a benefit in children and patients treated within 6 weeks of diagnosis	Currently being tested in prevention	9
Otelixizumab	III	272	No effect	Dose too low	Unclear at present	38
GAD-alum	III	334	No effect	Highlights importance of basing phase III efforts on robust and convincing phase II results	Currently being tested in prevention	7,10
GAD-alum	II	145	No effect			
Abatacept	II	112	9.6-month delay in C-peptide loss	Temporarily delays C-peptide loss in the face of long-term administration, although an effect was observed 1 year after therapy cessation	Potential use in combinations	8,19
Prochymal (Osiris)	II	63	No effect	Targeting inflammation may be insufficient	Unclear at present	55
IL-2 and rapamycin	I	9	Disease acceleration	IL-2 dose not sufficiently low; concurrent administration of agents may be suboptimal	Use of very-low-dose IL-2 or IL-2 muteins	56
Teplizumab (Delay Study)	II	58	Preserved C-peptide at 12 months	Teplizumab can attenuate C-peptide decline up to 8 months after diagnosis; effect strongest in children	Currently being tested in prevention	20
hOKT3γ-1 (Ala-Ala) (AbATE trial)	II	83	Preserved C-peptide at 24 months	Results consistent with previous studies showing an effect of anti-CD3 in T1D	Teplizumab currently tested in prevention	*
Anakinra	II	51 analyzed	No effect	Targeting inflammation alone at this advanced disease stage may not be sufficient to have an impact on disease progression	Unlikely to be used in T1D	45
Canakinumab	II	71	No effect		Potential use in combination or prevention	46
DiaPep277	III	457	Preservation of C-peptide at 24 months; more effective in adults	The effect was observed only with the use of GST and not apparent with an MMTT; mechanism may be through TLR-2 activation rather than antigen-specific modulation	Second phase III trial ongoing	12,13

GST, glucagon stimulation test; MMTT, mixed-meal tolerance test; TLR-2, Toll-like receptor 2. *K. Herold, personal communication.

results in accordance with that observed in the phase II trial (9). These results were further confounded by the conduct of the multisite trial in countries with a different standard of care for diabetes, which proved a serious challenge for attaining the primary trial end points (9). With these lessons learned, changes must occur in the way we operate; that is, the chance for success would be improved through appropriate address of a series of key questions.

WHAT ARE THE OUTSTANDING QUESTIONS TO ADDRESS?

What clinical outcomes should be targeted? The ultimate goal of interventions in new-onset T1D is restoration of durable insulin independence, an end point understood and appreciated by all. However, this ambitious goal will likely require combination therapies, including intensive insulin therapy, to optimize glucose control. One may modestly predict that even temporary (meaning a few years) preservation of C-peptide may prove to have clinical impact. The Diabetes Control and Complications Trial (DCCT) demonstrated that preservation of endogenous insulin production (as assessed by serum C-peptide level) was associated with lower HbA$_{1c}$ levels and fewer hypoglycemic events and microvascular diabetes complications over time (40). Thus, a strong case has been made to regulators for the importance of pursuing immunotherapy trials that lead to preservation of C-peptide, and regulatory agencies have adopted preservation of C-peptide as one end point for new-onset T1D trials. However, one unsettled question includes the duration of C-peptide preservation that will need to be achieved with interventions to gain approval from regulatory agencies and adoption by payers and providers. In the long term, it will be important to correlate preservation of C-peptide with improved clinical outcomes, such as short-term and long-term insulin dose requirements, HbA$_{1c}$ level, glycemic variability and time in range, frequency of hypoglycemia, and decreased occurrence of microvascular and macrovascular complications.

The ultimate therapeutic goal in prediabetes should be to prevent onset of insulin dependence. Even a delay in disease onset by 2–5 years could offer profound clinical benefits. Expeditiously realizing these challenging goals will require substantial and concomitant progress on several key fronts, including the development of a cost-effective, population-wide screening to identify at-risk individuals; improved biomarkers and approaches for staging disease

progression; and clinical testing of therapeutic agents with acceptable safety profiles in this setting, which offers a better opportunity than the recent-onset setting to modify disease progression because of higher endogenous β-cell reserves. The clinical development path for secondary prevention would also be facilitated and accelerated by changing the formal criteria for diagnosis of T1D and the clinical evaluation of insulin replacement in the at-risk setting, where the staging and prediction of insulin dependence is becoming increasingly more precise (41).

How can clinical trial design be optimized? Phase III trials should not be launched without a good understanding of the mechanism of action of the agent and evidence that the agent displays its predicted immunoregulatory effects in T1D. Optimal dosing and timing of administration must be identified before conducting phase III trials. Prognostic biomarkers to aid in determining which subjects will respond to an agent and predictive biomarkers indicating immunologic responses to the agent must be identified for clinical development. In clinical trials of recent-onset T1D, both immunologic effects and downstream effects on C-peptide preservation (influenced by many variables, including residual C-peptide and timing after diagnosis) must be assessed to understand whether lack of efficacy reflects a primary lack of immunologic effects of the agent. Small sample size and short mechanistic-oriented immunotherapy trials that explore effects in subsets of patients in order to tailor interventions and develop biomarkers must be prioritized. These recommendations are even more significant for prevention trials because of the current complexity (identifying at-risk individuals) and length (5–10 years) of study. Pilot studies in very-high-risk individuals that use intermediate end points of progression, such as reversal or prevention of dysglycemia rather than disease onset, will allow a much more rapid assessment of therapies that can subsequently be tested in fully powered prevention trials.

Our current understanding of the pathogenesis and heterogeneity of human T1D is still limited and must be addressed. Studies of cadaveric donor pancreata (e.g., JDRF Network for Pancreatic Organ Donors with Diabetes [nPOD]) from the at-risk and new-onset settings have shown a high degree of variability in the level of inflammation and presence of residual β-cells (42). In fact, it is quite striking how little inflammation is present in the pancreas of at-risk donors with multiple autoantibodies, which may call into question some therapeutic approaches being evaluated or under consideration. If T1D is a relapsing-remitting disease, a concept that has not been well explored, then should therapies be targeted to inducing and maintaining a remission, and can we identify biomarkers of such to guide clinical development and evaluation of these therapies? In developing immunotherapies for T1D, greater attention needs to be given to how the β-cell itself influences the autoimmune response by generating cytokines and chemokines and expressing costimulatory molecules and autoantigens. β-Cell stress, in fact, is likely important in initiating and perpetuating autoimmunity through some or perhaps all of these routes. In summary, immunotherapy ultimately will be part of a combination of therapies targeting inflammation, autoimmunity, β-cell stress and survival, and glucose control to deliver on insulin independence.

Which agents should be used in future studies? Given the previous discussion, it would appear obvious that agents that can quickly control the destruction of β-cells

and at the same time provide durable effects without causing long-term immunosuppression are likely among the best candidates for refined monotherapy protocols (e.g., improving patient selection, adapting the treatment for the young pediatric population). This said, the issue of implementation of new phase III trials remains. Specifically, these trials are problematic in their logistics (e.g., cost of operation, restrictions on clinical testing in children where the effect is most dramatic) and the uncertainty among investors and pharmaceutical companies resulting from the aforementioned trials not meeting their end points.

Hence, it may be worthy to perform combination treatments using one of the available immunosuppressive treatments or tolerogenic agents followed by a potential protolerogenic agent (e.g., a β-cell autoantigen). For example, a case can be made for testing antiinflammatory agents as a component of combination therapies because there is compelling evidence to show that inflammation is concomitant to T1D onset and may be involved earlier in the disease process (2). Encouraging pilot data have been reported on blockade of tumor necrosis factor-α (TNF-α) using etanercept (a recombinant soluble TNF-α receptor fusion protein) in children with new-onset T1D (43). From baseline to 24 weeks, the change in C-peptide area under the curve showed an improvement in the treated group associated with a corresponding decrease in insulin needs. Blockade of IL-1 is also undergoing testing, with data recently reported in settings of new-onset T1D using anakinra (a recombinant nonglycosylated form of the human IL-1 receptor antagonist) (44,45) or canakinumab (a fully human anti–IL-1β monoclonal antibody) (46). Unfortunately, neither agent showed efficacy in slowing C-peptide decline after T1D onset, underscoring the aforementioned need for combination therapies and earlier use in the disease, such as testing in prediabetes. In fact, recent data from NOD mice show a rapid and synergistic disease reversal following coadministration of anti-CD3 and anti–IL-1 at disease onset (47).

Another interesting approach in terms of mechanism involves the use of mobilizing agents, such as granulocyte colony-stimulating factor (G-CSF), that are endowed with immunoregulatory properties. In particular, it has been shown that G-CSF prevents onset of T1D in NOD mice by inducing tolerogenic DCs, thereby facilitating the expansion of regulatory T cells (Tregs) (48,49). Interestingly, G-CSF also synergizes with antithymocyte globulin (ATG) to reverse established T1D in animal models (37) and is currently being evaluated in a pilot clinical trial. Finally, it should also be mentioned that cell therapy approaches based on the use of in vitro expanded Tregs showed promising results in NOD mice and presently represents a very active field of translational research (50–52).

Which subjects should be included in the trials? Another crucial issue is the selection of the subjects to be treated. Presumably, once a treatment is approved, it will show effectiveness in a certain fraction of individuals at different stages of disease—prediabetes, recently diagnosed, established diabetes, and even latent autoimmune diabetes of the adult. However, in initial studies, it is preferable to focus on patient subgroups that will most likely lead to a robust proof of concept in terms of activity and feasibility before addressing indications where patients are more heterogeneous, potentially leading to a dilution of the therapeutic effect.

To further illustrate this point, in the case of clinical studies with anti-CD3, a greater benefit was observed in

subjects with the highest functional β-cell reserves (33). Secondly, TrialNet has recently completed a meta-analysis of C-peptide loss during the first 2 years after diagnosis of T1D in nearly 200 subjects that underscores the individual variability and age effects of decline in C-peptide after diagnosis of T1D. The results show that two thirds of individuals have significant levels of C-peptide (>0.2 pmol/mL) 2 years after onset (53). Other studies (e.g., DCCT) have demonstrated that only about 10% of individuals preserve this level of residual β-cell function at 5 years after disease onset. These findings suggest that in addition to the metabolic effects of insulin replacement in the new-onset setting, insulin is likely decreasing β-cell stress to allow recovery of dysfunctional β-cells. With more-aggressive metabolic control at the time of diagnosis, as is being investigated in the TrialNet Metabolic Control study, the acute decline of C-peptide after diagnosis may be even more blunted, which will raise the bar for demonstrating efficacy of immunotherapies. The TrialNet data also revealed that the decline in C-peptide was faster for subjects <21 years of age, and the younger subjects had lower starting levels of C-peptide around the time of diagnosis than the older subjects. This finding will need to be taken into account in the design of clinical trials. The fast decline in C-peptide in younger subjects suggests that interventions may need to be rapid and robust in their activity to demonstrate efficacy in that age-group; it further suggests that smaller studies may prove more feasible in younger subjects than in older subjects (53).

For the time being, we propose a focus on two clearly identified situations: recent-onset diabetes and pre-diabetes. In the former setting, interventions are needed for younger subjects, especially in the 1–5 years of age group. This group has the fastest growing age incidence in Europe, where extensive data have been collected over several decades (54). In the latter setting, the selection of individuals based on suitable biological markers of progression can predict the time frame during which individuals are likely to progress to an intermediate end point (increasing HbA$_{1c}$ level, decreased C-peptide level, etc.) or

insulin dependence, which may allow the design of smaller and faster trials. Safety should be of the highest consideration in this vulnerable patient population. With that in mind, some agents could be evaluated quickly in the new-onset setting for safety in not accelerating the loss of functional β-cell mass before testing in the at-risk setting.

REGULATORY, PAYER, PROVIDER, AND PATIENT ADOPTION PERSPECTIVE

A major challenge will be to demonstrate to regulators and payers that preservation of C-peptide in T1D, even for a limited period of time, with immune interventions provides clinical benefit. It will be essential to propose strategies that are based on disease modification and a good scientific understanding of the mechanism of action of the therapy. For their adoption by providers and patients, immunotherapies must be widely accessible, practical in their administration, and offer a vital and clearly understandable improvement over the current standard of care while still having a reasonable safety profile. For individuals who are being followed prospectively in the at-risk setting, the definition of diabetes and insulin dependence needs to be modified to set the stage for clinical trials, regulatory approval, reimbursement, and adoption. Sophisticated prognostic risk scores of staging and progression in the at-risk setting are being developed and will justify and guide early interventions in that setting. Once validated, these staging approaches may provide intermediate end points for clinical trials that can be recognized by regulatory authorities.

Biotechnology and pharmaceutical companies must continue to play a vital role in getting new therapeutics on the market. Ideally, the commercial and academic sectors should partner more closely around designing and conducting clinical trials. Further, these groups should work with regulatory authorities to ensure in-depth understanding of the natural history of T1D and potential risk-benefit of interventions and to develop transparent regulatory guidance for interventions in the recent-onset

Key Emerging Questions

1. How can clinical trials be best designed?

2. What is the precise mechanism of action of therapeutic agents?

3. How can biomarkers be developed, validated, and integrated into clinical trials?

4. What is the definition of *benefit/success*?

5. How can the best therapeutic combinations be determined?

6. How critical is it to integrate β-cell therapies with immune therapies to reverse T1D?

7. How can industry, academia, regulators, and funders work together more effectively?

8. How do we communicate emerging clinical research trends to regulatory agencies more effectively?

9. How do we educate payers?

10. How do we keep constituents in the game with trials that are presumed failures?

FIG. 3. Key emerging questions in the field of T1D prevention and reversal.

Key Recommendations

1. Continue to develop and evaluate immune interventions for new-onset and at-risk T1D, with simultaneous development and validation of prognostic and predictive biomarkers.

2. Establish a C-peptide database.

3. Change the criteria for the definition of T1D in the at-risk setting.

4. Foster more effective collaborations among diabetes organizations, individuals and families, academia, industry, and regulatory authorities.

FIG. 4. Key recommendations to improve efforts, moving forward, in terms of immunotherapies directed at attenuating T1D.

and at-risk setting. Both the commercial sector and the field will need to embrace proper phase II dose ranging studies and the identification and validation of prognostic and predictive biomarkers to enhance chances for successful clinical development.

RECOMMENDATIONS AND CONCLUSIONS

Based on a careful evaluation of T1D intervention efforts, 10 key questions (Fig. 3) emerge as being essential to facilitate and hasten translation of immunotherapies in T1D. These questions focus on five main areas related to trial design (including safety and efficacy matters), biomarkers, regulatory, reimbursement, and patient issues. Each one represents a major challenge in itself and will likely require significant community input to adequately solve the underlying need. Beyond community input, the implementation of four recommendations (Fig. 4) would also likely aid in this effort.

The first recommendation endorses the continued development of immune interventions for new-onset and at-risk settings of T1D. The second involves establishing a database of deidentified, placebo-controlled C-peptide data from new-onset T1D trials conducted to date by both academia and industry. These data would be used to generate a standard curve of the rate of fall of endogenous insulin production (as measured by loss of C-peptide) by age during the first 2 years after T1D onset. The third recommendation proposes a consensus statement of the criteria for diagnosis of T1D in the at-risk stage of the disease, and the fourth is to foster closer and more-effective collaborations with regulatory authorities. Finally, the clinical development of T1D immunotherapies would be impossible without the central contribution, dedication, and participation of the community of patients and their families. Indeed, this needs to be a main priority because enrollment before disease onset will require an intensive degree of patient-provider cooperation.

A growing body of literature supports the notion that immune intervention can attenuate and, in some cases, temporarily halt autoimmune diabetes. However, implementation of a variety of recommendations and parameters as outlined previously would improve the chance of their successful development. The diagnosis of T1D should be treated as a medical emergency in which metabolic control currently and immunoregulation in the future will need to be quickly established to preserve residual β-cell function. In the at-risk setting, immune therapies will be used to prevent insulin dependence, and if anything, immune therapies will likely prove to be more effective in that setting in the context of higher endogenous β-cell reserves. Combination therapies should be developed and

optimized to have the most robust impact on clinical outcomes, especially to induce durable insulin independence, which needs to be the long-term goal. Although recent results have raised concerns about sustained pharmaceutical industry commitment, the development of prognostic and predictive biomarkers and the ability to identify a subset of at-risk individuals who will be insulin dependent in a relatively brief period of time will catalyze continued industry involvement. Insights into immunomodulation in T1D will continue to be provided by data emerging from trials currently under way (Fig. 1 and Table 1). Furthermore, future clinical development and clinical trials in T1D will be aided and informed by the multiple ongoing natural history studies (e.g., TrialNet, JDRF nPOD, T1D Exchange) that are providing new insights into the immunopathogenesis and heterogeneity of the disease and by the identification and validation of biomarkers. Immune intervention can and will have a meaningful impact in T1D. To ensure this, the T1D research community must proceed with renewed optimism and a more thoughtful and innovative approach to clinical trial design and with strengthened collaborations among all key stakeholders, including academic investigators, industry, regulators, patients, health-care providers, payers, and funders. Delivering on effective immunotherapies for T1D will require perseverance and constant interplay between the bench and the bedside.

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