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Efforts to Prevent and Halt Autoimmune Beta Cell Destruction

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Synopsis

Despite improvements in our understanding of the natural history of type 1 diabetes (T1D), an intervention capable of consistently and safely preventing or reversing the disease has yet to be developed. The inability to cure this disorder results, to a large extent, from the complex pathophysiology of T1D, continued struggles to identify its precise etiological triggers, and voids in our understanding of the immunological mechanisms that specifically target pancreatic β cells. Interestingly, rapidly improving technologies for managing T1D render discussions surrounding equipoise of vital importance, especially when considering interventions deemed of “high-risk” in terms of their safety. This chapter reviews the conceptual basis for prevention versus intervention trials in settings of T1D, past experiences for clinical trials seeking such purposes, controversial issues to disease interdiction, and seeks to provide a roadmap for future efforts seeking to cure this disorder.

Keywords

Type 1 Diabetes; Intervention; Prevention; Combination Therapy

Prevention versus Intervention

One of the greatest philosophical and logistical challenges in designing studies aimed at interdicting T1D lies in deciding whether to focus the major effort on prevention or intervention¹. To some, this may be considered a semantic argument surrounding the usage of the terms prevention and intervention; but in fact primary prevention (i.e., prevention of autoimmunity), secondary prevention (i.e., prevention of overt hyperglycemia in subjects with established autoimmunity), and intervention studies (i.e., studies aimed at preservation of C-peptide rather than true reversal) are quite unique from each other. When one attempts to design studies aimed at interdicting T1D, each of the aforementioned windows of opportunity possesses a particular set of strengths and weaknesses. Perhaps more telling of

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the ongoing struggle to choose a central paradigm for T1D interdiction is the fact that primary prevention, secondary prevention, and intervention studies are all currently being performed as part of large multicenter trials.

Despite ongoing debate regarding optimal study design, consensus exists that acting early (i.e., primary prevention) likely represents the best opportunity for effectively eradicating T1D². However, the ability to accurately predict those destined to develop T1D improves as the presumed capability to effectively intervene declines (Figure 1)³. With this, potential therapies for primary prevention of T1D must be extremely safe, since they would be provided to subjects who may never actually develop the disease. Beyond this, the ability to perform prevention studies, as they are currently conceived, are also hindered in that they require complex and massive screening efforts to identify subjects who are potentially eligible. For all of these reasons, prevention studies are inherently difficult to plan and costly to execute. Were one to eliminate screening and move to a model of universal prevention, the difficulties of screening would be markedly reduced, but concerns over equipoise would, once again, be raised to levels beyond those wherein individuals of elevated risk are identified and subjected to intervention.

In contrast to these considerations, informing newly diagnosed T1D patients regarding opportunities to participate in intervention trials provides a far higher yield and lower cost paradigm for identifying and enrolling subjects in clinical trials. That said, such trial designs carry less likelihood for success, given the reduction of existing beta cell mass and established and aggressive autoimmunity in patients already diagnosed with T1D. Ultimately, attempts to interdict the disease process at almost any point can logically be defended as long as the therapeutic agents are chosen with a thorough appreciation of relative risk and benefit. With this in mind, low risk therapies can ethically be tested in prevention studies with large numbers of subjects, but are expensive and require many years to document effect. Conversely, high risk therapies are more rightly reserved for intervention studies with smaller numbers of subjects who have T1D, and require only 1–2 years to document potential efficacy. To ensure a state of equipoise between risk and benefit, intervention studies in recent onset patients have emerged as the model for studying immunomodulatory and immunosuppressive therapies with potentially significant side effect profiles. Conversely, prevention studies remain focused on lower-risk therapies that can be applied to larger populations.

While space limits an extensive discussion of every agent previously used and those currently in use in T1D prevention and intervention studies, we will detail a number of therapies being investigated and briefly mention several that have provided important lessons in the quest for developing a cure. The prevention of recurrent autoimmunity is absolutely key for a sustained disease reversal, should effective means to replace islet cell function be developed.

Prevention Strategies

Improvements in our understanding of the natural history of T1D, combined with markers identifying stages of “pre-type 1” diabetes, have lead to the development of different windows of opportunity interdict the disease process (Figure 1). Still, to implement effective prevention strategies we will clearly require a far greater understanding of the immunologic, genetic, and environmental mechanisms leading to T1D. Previous and ongoing prevention efforts have focused primarily on the use of low-risk antigen specific therapies. While these efforts have, to date, been unsuccessful in achieving their primary goal of prevention, they have undoubtedly succeeded in establishing international multicenter T1D research

collaborations and have markedly improved our understanding of the disease's natural history.

Insulin

Insulin has long been investigated as an autoantigen that might be manipulated in order to augment the natural history of T1D. Based on early studies in the NOD mouse⁴ demonstrating that early exposure to oral insulin in these high risk animals was effective in preventing diabetes, as well as promising pilot studies in other autoimmune diseases demonstrating oral tolerance, the Diabetes Prevention Trial–Type 1 (DPT-1) (NCT00004984) was organized to determine if either subcutaneous or oral insulin could prevent or delay the onset of T1D through the immunomodulatory effects of recurrent exposure to insulin. Performed in the late 1980s and early 1990s, DPT-1 was one of the first large multicenter, randomized, placebo-controlled trials to attempt prevention of type 1 diabetes in high-risk patients. The DPT-1 screened over 100,000 first and second degree relatives of T1D patients in order to identify less than 3,500 subjects who were islet cell cytoplasmic autoantibody (ICA) +/- insulin autoantibody (IAA) positive. Of these, 339 were enrolled in the parenteral arm and 372 in the oral insulin arm. While both oral and parenteral insulin demonstrated excellent safety profiles, the DPT-1 failed to demonstrate therapeutic benefit for either investigational approach. However, the study did prove that a large multicenter T1D collaborative was feasible and as a result, the predominantly National Institute of Health (NIH)-funded TrialNet was established. This result having been said, a post-hoc review of DPT-1 data demonstrated that at-risk patients (i.e., 5-year risk of 25–50%) who received oral insulin and had high IAA levels experienced a considerable delay in the onset of T1D⁵. As such, TrialNet has designed an appropriately powered follow-up study to determine if oral insulin can indeed delay the onset of T1D in those intermediate risk individuals with two or more islet autoantibodies, one of which is IAA (NCT00419562). Relatives of T1D patients are currently being screened to determine if they qualify for participation in the oral insulin study by participating in the TrialNet natural history study, which aims to identify and track patients at risk for developing T1D (NCT00097292).

Because insulin is a likely target autoantigen in the disease, similar studies focusing on achieving tolerance by alternative mechanisms of insulin delivery have been explored by other study groups. The Finnish Diabetes Prediction and Prevention Project (DIPP), in which intranasal insulin was administered to genetically at-risk autoantibody positive subjects, failed to demonstrate a benefit⁶ (NCT00223613). The Australian Intranasal Insulin Trial (INIT I), a safety study performed in adults, documented immune changes consistent with mucosal tolerance to insulin⁷. INIT II is now underway and is evaluating a larger population, by determining the effect of different doses of intranasal insulin in patients to prevent or slow the onset of T1D⁸ (NCT00336674). In addition, the Primary Oral/Intranasal Insulin Trial (Pre-POINT) will be attempting primary prevention in a dose finding study, to provide oral or intranasal insulin to genetically at risk infants who have not yet developed T1D associated autoantibodies⁹. Recently, interventional efforts using insulin B-chain immunotherapy in newly diagnosed T1D patients were reported demonstrating specific T cell responses to the non-metabolically active insulin, but no effect on C-peptide, when compared to placebo.¹⁰

Glutamic Acid Decarboxylase 65

Glutamic acid decarboxylase 65 (GAD65) is another autoantigen that has been targeted for potential therapeutic use in T1D. Similar to insulin, strong pre-clinical data from the NOD mouse¹¹ suggest that prevention following vaccination with GAD65 is possible. Early safety and dose finding studies of GAD65 (Diamyd®) were performed in adult patients having latent autoimmune diabetes (LADA), with subjects receiving two subcutaneous

doses of GAD65 (4, 20, 100, or 500 μ g) or placebo. Subjects were followed for 24 weeks, with no adverse events being noted. In addition, the 20ug dose appeared to demonstrate preservation of endogenous beta cell function. A follow-up phase II trial, this time involving 70 children (10–18 years) with T1D, demonstrated preservation of beta cell function with no treatment related adverse events¹² (NCT00435981). Interestingly, T1D subjects that received 20 μ g of GAD65 had fasting C-peptide levels at 24 weeks which were increased compared with placebo, as well as an increased fasting and stimulated C-peptide level from baseline to 24 weeks¹². Earlier administration (i.e. within 6 months of disease onset) appeared more efficacious, albeit the number of such subjects were limited. Based on these encouraging phase I and II data, TrialNet is currently performing a phase III placebo controlled randomized trial of GAD65 in newly diagnosed T1D patients (NCT00529399). Similar industry sponsored studies are being conducted concurrently in Europe and the United States. A GAD65 prevention study is being planned in individuals screened through the TrialNet natural history study who are found to be GAD autoantibody positive.

Intervention Strategies

As opposed to the antigen specific efforts noted in prevention trials, the majority of early T1D intervention strategies have employed immunosuppressive regimens to control autoimmunity and preserve beta cell function. These studies have been performed with relatively few new onset T1D patients and when undertaken, were done so with drugs such as azathioprine,¹³ cyclosporine^{14, 15}, and antithymocyte globulin along with prednisone¹⁶. Many of these immunosuppressive agents showed initial promise in preserving C-peptide, but were none-the-less abandoned due to intolerable side effect profiles and limited efficacy. In contrast, agents such as nicotinamide¹⁷, ketotifen¹⁸, and Bacille Calmette-Guerin (BCG),¹⁹ all proved to be low-risk, but also failed to demonstrate benefit in preserving beta cell function. Additional low-risk non-antigen specific therapies such as alpha-1 antitrypsin²⁰, autologous umbilical cord blood infusion plus docosahexaenoic acid (DHA) and Vitamin D3 supplementation²¹, heat shock protein derived DiaPep22722, and avoidance of cow milk proteins (TRIGR)²³ are currently being investigated. Nevertheless, as we struggle to develop both safe and effective therapies, we may be forced to accept the paradox that therapies with the immunological power to effectively reverse T1D may already exist but may only be able to succeed at the cost of inducing potential short and long term side effects profiles that are worse than living with diabetes.

Anti-CD3

Depletion of auto-reactive T cells is a logical approach to interdicting the disease process in T1D. Pre-clinical data from the NOD mouse have demonstrated that monoclonal antibodies to CD3 are capable of both preventing and reversing diabetes^{24, 25}. Two different anti-CD3 products, hOKT3gl (Ala-Ala/Teplizumab) and ChAglyCD3 (TRX4/Otelixizumab) have recently been employed in human intervention studies (NCT00378508 and NCT00451321, respectively). While leading to short term T cell depletion following administration, anti-CD3 antibodies may selectively increase the production of regulatory T cells thought to counter the effector T cell response responsible for islet destruction in settings of T1D. Published studies of anti-CD3 therapy have been promising and suggest there may be preservation of C-peptide for as long as 18–24 months after therapy^{26, 27}. This said, depending on the protocol, current dosing regimens require a 6–14 day IV infusion; a requirement that may limit both patient enrollment and possible wide scale use of this agent. Safety issues include the commonly occurring cytokine release syndrome after initial dosing, rashes, reactivation of EBV, potential formation of antibodies to anti-CD3 as well as unknown long-term side effects. Larger studies of anti-CD3 are currently being performed by the two manufacturers of these monoclinal antibodies. In addition, TrialNet is

implementing an anti-CD3 prevention study in very high risk non-diabetic relatives (i.e., those with two or more islet autoantibodies plus evidence of impaired glucose tolerance).

Anti-CD20

The anti-CD20 monoclonal antibody Rituximab (Rituxan®), down-regulates B lymphocyte signaling of T cells and therefore, may reduce the ability of cytotoxic T cells to induce islet injury, in settings of T1D. Rituximab is one of several agents chosen as part of the aforementioned paradigm which focuses on agents that have already demonstrated benefit in other human autoimmune disease. That said, preclinical data with anti-B-lymphocyte activities have also demonstrated efficacy in preventing and reversing diabetes in the NOD mouse^{28, 29}. Now part of the standard therapeutic armamentarium for rheumatoid arthritis, non-Hodgkin's lymphoma, and transplant rejection; Rituximab has also shown recent promise in the treatment of lupus and multiple sclerosis. Within TrialNet, Rituximab was administered to new-onset T1D patients within 100 days of diagnosis in a randomized, placebo controlled trial to determine if four weekly IV infusions safely preserve C-peptide. Preservation of C-peptide was noted one year after Rituximab was administered (mean AUC c-peptide 0.56 pmol/mL versus 0.47 pmol/mL on placebo) (NCT00279305). While adverse events were also more common in the drug treated subjects, the large majority of events were grade 1 or grade 2 infusion reactions that were observed primarily during the first infusion. No increase in infection rates or neutropenia was observed in those who received Rituximab. While these data are encouraging in their support of the notion that B lymphocytes can be augmented to partially interdict the autoimmune process, data from the two year time point are eagerly awaited and will have to be carefully considered in determining future therapies.

Mycofenolate Mofetil (MMF) and Anti-CD25

As noted in the aforementioned examples, no single agent has demonstrated an ability to indefinitely preserve C-peptide production in new onset T1D subjects. Guided by the successes seen in cancer and HIV, combination or "cocktail therapy" that simultaneously use multiple agents at lower doses has been proposed as a model to improve efficacy while limiting likelihood of therapeutic side effects. One of the first examples of combination therapy to treat T1D was recently investigated as part of the TrialNet consortium; Mycofenolate Mofetil (MMF) and Daclizumab (DZB/Zenapax®) (NCT00100178). Both agents have previously been used successfully in other human autoimmune settings and also demonstrated efficacy in animal models of T1D³⁰. The rationale for the selection of these agents was based, in part, on safety profiles along with their presumed mechanisms of action. Specifically, the immunosuppressive profile of MMF combined with the depletion of activated T cells provided by DZB. The MMF/DZB combination tested within the TrialNet involved a single IV infusion of the DZB antibody and daily oral therapy with MMF administered to new-onset subjects. The study included three arms: MMF and DZB combination therapy, MMF monotherapy, and placebo. Unfortunately, neither MMF-alone nor MMF in combination with DZB had an effect on the loss of C-peptide in subjects with new onset T1D.³¹

Cytotoxic T-Lymphocyte Antigen-4 Immunoglobulin

Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4) is expressed on the surface of T helper cells and transmits an inhibitory signal to T cells by blocking the stimulatory effect of CD28 binding^{32, 33}. In addition, CTLA-4 may play an important role in the function of tolerance inducing regulatory T cells. Furthermore, polymorphisms in the CLTA-4 gene are known to associate with autoimmune diseases, including T1D³³. As such, CTLA-4-Ig is a selective T cell costimulation modulator and has been extensively investigated and has already gained FDA approval for the treatment of rheumatoid arthritis (Abatacept/Orencia®). Using similar

rationale, CTLA-4-Ig has been proposed as another potential non-antigen specific therapy for T1D. Currently, the TrialNet consortium is performing a randomized, double-blind, placebo controlled trial of CTLA-4-Ig/placebo in recently diagnosed T1D patients (NCT00505375). Because CTLA-4-Ig is administered as a monthly IV infusion, participation in this study required considerable commitment from patients, their families, and research staff. Nevertheless, the side effect profile is well described and reasonably tolerable, with enrollment completed for the TrialNet effort in 2009. Data are expected to be reported from this study regarding safety and efficacy in the T1D population in 2011.

Anti-Thymocyte Globulin

Anti-Thymocyte Globulin (ATG) is a polyclonal anti-human T cell antibody preparation produced by inoculating rabbits or horses with human thymocytes³⁴. ATG has long been a critical part of preparative regimens for transplantation and cancer therapy as it results in non-specific T cell depletion³⁵. Recovery from T-cell depletion following ATG therapy has been associated with a rebalance of the number of effector versus regulatory T-cells and therefore, it offers a potential advantage in resetting the immune system in patients with autoimmunity³⁶. As but another example of a powerful non-antigen specific agent, ATG has been used either alone or in combination in the treatment of a variety of autoimmune conditions, including Wegner's granulomatosis, lupus, rheumatoid arthritis, multiple sclerosis, scleroderma, aplastic anemia and myelodysplastic syndrome, and even T1D³⁷⁻⁴⁶. In terms of side effects, ATG therapy has been associated with cytokine release syndrome as well as serum sickness. While not trivial, these side effects are tolerable; especially when ATG is administered at lower doses than those typically used in transplantation and cancer therapies. While definitive data are still awaited, a small European study using one commercial form of ATG (ATG-Fresenius) demonstrated potential efficacy and tolerance of ATG related side effects⁴⁶. In addition, an ongoing study a second commercial form of ATG (Thymoglobulin®) is being performed by the NIH Immune Tolerance Network utilizing recently diagnosed T1D patients (NCT00515099).

Anti-Thymocyte Globulin (ATG) and Granulocyte Colony Stimulating Factor (G-CSF)

While ATG monotherapy appears promising, consistent with our aforementioned concept supporting combination therapy, we consider it likely that an ATG based protocol that includes a second agent, G-CSF, may have even greater potential for preservation of beta cell mass. Perhaps the best support for this assertion comes from data generated in Brazil in which young adults with very recent onset T1D received cyclophosphamide, G-CSF, and ATG in what was termed a non-myeloablative auto-transplantation⁴⁷ (NCT00315133). The idea of immune depletion followed by regulatory T cell mobilization or re-infusion, a mechanism deemed likely to result from this therapy, has strong pre-clinical data to support the assertion that such an approach may be able to ameliorate autoimmunity⁴⁸. While subjects who received this combination therapy experienced considerable morbidity (e.g., neutropenia, alopecia, testicular dysfunction, etc), they also benefited from a remarkable degree of therapeutic efficacy. Twenty of 23 treated subjects experienced at least one month of insulin independence, with the majority being insulin free for over a year. This study also represents one of the first reports of a sustained increase in the stimulated C-peptide values in patients with T1D⁴⁷⁻⁴⁹. While their results are undeniably proof of the potential for aggressive immunoablative therapy in treating T1D, the side effect profile of this particular combination is unacceptable in the eyes of most physicians caring for children with T1D⁵⁰.

As our group has long supported the concept of safe combination therapies, we have attempted to deconstruct the Brazilian combination using the NOD mouse model to guide our development of a lower-risk therapy for humans. By excluding cyclophosphamide, and relying on a combination of only low dose ATG and G-CSF, we were recently able to

demonstrate a durable reversal of diabetes in over 75% of NOD mice; while ATG alone was only able to reverse disease in 33% of animals⁴⁸. In addition, we demonstrated that the combination therapy provided the most robust increase in regulatory T cells and, perhaps more importantly for clinical application, enabled reversal of diabetes at higher initial glucose values than ATG alone. Given these exciting pre-clinical data, our group has recently undertaken planning for an analogous human trial designed to study the safety and potential efficacy of low dose ATG (2.5mg/kg total dose) and 12 weeks of pegylated G-CSF therapy (Neulasta® 6mg every 2 weeks).

Cell Therapies

The concept of employing cell therapies to provide a quantity of islet cells capable of restoring euglycemia in patients with T1D has long been thought of as a potential panacea for ameliorating the disease. However, this notion remains largely unfulfilled, due to the pronounced shortage of cadaveric islets combined with the inability to overcome the primary autoimmunity underlying the disorder; a step one would deem necessary before such an approach will be even conceptually feasible.

However, over the past few years, the term “cell therapies” has undergone significant change in the T1D research arena as a number of groups have expanded this terminology away from exclusive reference to cell therapies designed to provide beta cell replacement (i.e., islet transplantation and stem cell differentiation) towards the concept of using cell therapies as a means to provide direct immunoregulatory therapy. Indeed, clinical trials designed to test the potential of a number of cell types having the capacity to modulate the immune response are currently underway in T1D patients.

Based on the observation that umbilical cord blood contains a dense population of highly potent regulatory T cells, our group recently completed a phase I study investigating the potential for a single autologous cord blood infusion to preserve C-peptide in young children with T1D. While our preliminary results regarding efficacy were inconclusive after one year, those studies did demonstrate that the approach was safe and resulted in short term increases in regulatory T cell frequencies^{21, 51}. Based on these results, a phase II study was recently initiated to determine the efficacy of a single autologous umbilical cord blood infusion, followed by one year of supplementation with high dose vitamin D and omega 3 fatty acids to preserve C-peptide (NCT00873925).

Another cell-type of great interest for its potential to provide immune regulation is the dendritic cell (DC)⁵². A primary function of DCs is to process antigenic material and present it on their cellular surface in a form recognized by other cells of the immune system. As such, they are a very logical target for designing cell based immune therapies. Preclinical data from the NOD mouse has already demonstrated proof of concept that manipulated DC's can effectively prevent T1D⁵³. With this concept and preclinical data, a phase I study has been initiated to determine if the injection of autologous modified DC's in subjects with T1D is safe and to look for any signals of tolerogenic immune response⁵⁴(NCT00445913).

Mesenchymal stem cells (MSC) have also piqued the interest of T1D researchers, given recent data suggesting their pronounced ability to afford immunoregulation in a variety of settings, ranging from autoimmune disease to graft-versus-host disease⁵⁵. MSCs are unique as a form of cell therapy in that they are thought, by most, to have little to no known allo-sensitivity. As such, in theory, MSCs from any donor can be provided to any recipient. Because MSCs are thought to provide localized suppression of immune response in areas of inflammation with a degree of functional activity that is quantitatively controlled by the severity of tissue inflammation, they are another logical choice for cell based immune therapy. While MSCs have a limited life span in vivo, this is potentially advantageous; given

concerns regarding the long-term risk of immortalized stem cells. In addition, MSCs can easily be re-dosed, due to their lack of inducing alloimmunity. Pre-clinical data from animal models of T1D have already demonstrated the ability of MSC infusion to promote beta cell repair, enhance insulin secretion, and facilitate islet allograft tolerance^{56, 57}. Enrollment for a phase II study using a commercially available MSC preparation (Prochymal®) in new-onset T1D patients was recently completed and safety and efficacy data are eagerly awaited (NCT00690066).

Beyond umbilical cord blood, DC, and MSC; other forms of cell based therapies are being actively considered for T1D. These would include, but not be limited to polyclonal regulatory T cells, antigen specific regulatory T cells, and well as T cells modulated in vitro to produce anti-inflammatory cytokines in vivo⁵⁸. As of this date, none of these efforts have seen actual therapeutic application in settings of T1D, but it is anticipated that if concerns over safety and feasibility are overcome, such trials will be undertaken. This, with support from pre-clinical efforts in NOD mice suggesting the ability of regulatory T cells to modulate T1D development^{56, 57}.

Learning from the Past to Predict the Challenges of the Future

Despite the formation of dozens upon dozens of clinical trials seeking to prevent or reverse T1D, the last 30 years have been characterized by the inability of such efforts to provide substantial prolonged benefit to patients. This lack of an effective intervention has also delayed population based screening for T1D as our ability to predict the disease in both higher risk relatives and the general population has seen marked improvement over this same time period (See Chapter X: Bonifacio and Ziegler). These trial “failures” are not without benefit, as they have taught us that a phase specific intervention, based on stage in the natural history of T1D, will likely be required for successfully interdicting in T1D. Many recently developed prevention and intervention studies exemplify another newly considered paradigm under which agents are not selected simply because of their therapeutic benefit in the NOD mouse model, but due to their providing established benefit in other human disorders considered of autoimmune origin. For example, drugs used to treat disorders such as rheumatoid arthritis, lupus, and multiple sclerosis can rationally be applied to T1D and, carry the additional benefit of having known safety and side effect profiles. Similarly, the paradigm or concept of combination therapy has emerged as the growing number of monotherapy failures suggests that the complexity of autoimmunity underlying T1D is far too complicated to control with single agents. We believe the simultaneous application of agents which individually provide immunosuppression, immunomodulation, and islet regeneration should improve future efforts seeking to intervene in T1D (Figure 2).

One recent charge from both the T1D research and lay communities has been to improve the pace of efforts seeking to identify a cure for T1D. While such motivation is laudatory, we would caution that as the field moves forward to test agents (especially combination therapies), the potential for side effects must continually be balanced against the benefits of prevention and intervention strategies. Beyond this, as the number of potential therapies subject to therapeutic trial continues to grow, an additional emerging challenge will be to decide how to choose agents for future interventional studies. Put another way, agents with equally strong rationale for inclusion have recently been suggested (e.g., anti-CD3, anti-CD20, etc.), but finite monetary and human resources limit our ability to employ every agent with solid rationale in a timely manner. While T1D is not an uncommon disease, the number of available subjects for prevention and interventional studies is not so large that we can simply design and fully enroll every potential study that could be designed. Thus, additional factors, such as ease of delivery, agent cost, previous experience in other autoimmune disease, need for screening (in cases of T1D prevention), and applicability to large numbers of patients must all be considered in appropriately rank-ordering potential interventions.

Finally, one of the greatest challenges that effects past, current, and future prevention and intervention studies is the proper interpretation of study data and comparison of outcomes between studies. While recent studies have improved to the point that it has becoming increasingly often where demonstrations of statistically significant changes in C-peptide over time occur (i.e., preservation), we must continue to ask ourselves if these changes are, in fact, clinically significant? Without the ability to point to clinically significant endpoints, it is our belief that patients will not likely show continued interest in such forms of therapy; especially if onerous in their delivery. As such, we must also continue to search for clinically meaningful endpoints. While the outright reversal or prevention of T1D is an easily understood endpoint, measurements of incremental metabolic improvements which guide us to that goal are less easily agreed upon. Peak, basal, and area under the curve (AUC) C-peptide are commonly used metabolic endpoints, but ones that do not adequately reflect complex changes in islet function. Interpretation of interventional data must also take into account the age of enrolled subjects. Many interventional studies enroll young adults in whom T1D has a very different natural history from the T1D observed children diagnosed with T1D at a younger age. Thus, application of even the most successful research interventions may not translate into similar clinical benefit for the majority of new onset T1D patients who eagerly await “proven” interventions.

Conclusion

The past 50 years have seen a rapid increase in knowledge of the epidemiologic patterns and natural history of T1D, insights that were anticipated to accelerate efforts seeking disease prevention as well as to allow for the development of a cure⁵⁹. And while it is also true that clinical care for patients with T1D has also improved, our failure to adequately understand the precise mechanisms leading to clinical disease as well as to develop a suitable intervention to prevent or reverse this disease has left open the goal of finding a cure for T1D. This said, future prevention and intervention studies must be designed with an appreciation for the lessons learned from previous efforts that have failed to deliver on their goal of providing a cure. One such example is that to date, single agent therapies with drugs chosen largely on the basis of their efficacy in animal models have failed to produce meaningful results. As a result, rationally designed combination therapies with agents targeting immunosuppression, immunomodulation, and islet regeneration may more logically represent the future of successful prevention and intervention trials. In addition, as diabetes management techniques continue to improve, the safety and efficacy of future interventions must be balanced with the real costs (i.e., physical, emotional, and monetary) of living with T1D.

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Figure 1. The "treatment dilemma" for type 1 diabetes

Many studies from animal models of type 1 diabetes in combination with a much more limited series of investigations in human beings suggest that early intervention not only is more effective in terms of disease prevention, but also often requires more benign forms of therapy. In contrast, the ability to identify an individual who will truly develop type 1 diabetes increases as the individual approaches onset of overt disease. Adapted from reference [3] with permission.

Figure 2. Combination therapies for the reversal of type 1 diabetes

The reversal of type 1 diabetes will likely require a combination of agents providing immunomodulation, immunosuppression, and beta cell regeneration. Newly diagnosed patients may achieve cure through combination approaches that control autoimmunity and protect remaining beta cells. Addition of agents which stimulate beta cell regeneration will likely be required to accomplish reversal in long term patients.