

Regulatory and policy issues for T1DM immunotherapy

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The development of immunotherapies for T1DM has lagged the development T2DM drugs, but with more clarity around regulatory requirements, large pharmaceutical companies have recently entered the field to support late stage programs. This clarity around regulatory expectations has emerged because of the convergence among regulators and clinical experts in how efficacy of these therapies should be assessed. The key agreement is that the primary efficacy endpoint for treatments directed at the underlying autoimmune cause of T1DM should be endogenous insulin secretion as reflected by standardized C-peptide measurements. Important secondary endpoints include glycemic control, total daily insulin dose and hypoglycemia rates. Most T1DM therapeutic development efforts are directed at new onset disease, which represents a small proportion of the entire T1DM population. A new frontier in T1DM therapeutic development is emerging around combination treatment of established T1DM, a population that far outnumbers those with new onset T1DM. Fully effective therapies of new onset or established T1DM will almost certainly require a combination of two or more therapies. A T1DM prevention vaccine will not be feasible until after extensive experience with the agent as a treatment of new onset and/or established T1DM.

Introduction

Jenner, Pasteur and other icons in the early history of vaccine development could not have imagined the potential of inducing the immune system to fight non-infectious chronic diseases like T1 diabetes (T1DM). Even just over a decade ago, the importance of inflammation and associated cytokines in the pathogenesis of Type 2 diabetes (T2DM) was unrecognized. Today, the prospects of vaccine-like therapies for T1DM and immunomodulatory approaches for both T1 and T2DM are upon us. Insulin deficiency is no longer the single common thread connecting both major forms of diabetes. Inflammatory cytokine pathways are implicated in and targeted with the same drug for both T1 and T2DM.¹

This summary focuses on regulatory and policy issues pertaining to immune approaches aimed at T1DM though overlap

with T2DM continues to grow in the therapeutic development world. Emphasis is also placed on antigen related approaches though the line between classic vaccine-like approaches and those that modulate the immune system through non-antigen mechanisms is increasingly blurred. Indeed a continuous spectrum of therapeutic approaches is emerging that stretches from small molecule anti-inflammatory agents to peptide auto-antigens like insulin and glutamic acid decarboxylase (GAD). While the United States Food and Drug Administration (FDA) is also a focus, this is arbitrary and increasingly unjustified because the European market and regulatory system are approaching parity in importance to the US counterparts.

Regulatory Background

FDA has evolved its general approaches to therapeutic vaccines for non-infectious diseases and its specific approaches to therapies directed at the underlying autoimmune cause of T1DM. Therapeutic vaccines for cancer remain under the regulation of the Center for Biologics Evaluation and Research (CBER),² though the first, and to date the only, approval of a cancer vaccine was issued from the unit within CBER that is responsible for cell based and gene therapies—and not the unit that regulates classic vaccines.³ A guidance on therapeutic cancer vaccines has been issued by FDA,⁴ but no specific guidance has been issued for T1DM immunotherapies.

Indeed, T1DM immunotherapies have been, and for the foreseeable future will continue to be, regulated by the Division of Metabolic and Endocrine Products (DMEP) within the Center for Drug Evaluation and Research. DMEP is responsible for conventional glucose-lowering drugs—both small molecules and peptides like insulin and glucagon-like peptide 1 (GLP-1) analogs. Even the earliest regulated attempt at a preventative T1DM therapy using the auto-antigen, insulin, was hosted by DMEP.⁵

This regulatory background is not inconsequential because different approaches to manufacturing and testing drug and biologic products have evolved at FDA. Some of these are driven by real scientific differences between the paradigms of drug therapy and vaccines. For example, establishing the relationship between drug dose and its desired and undesired responses is not as feasible or important for classic vaccines, which typically involve very small amounts of antigen exposure and near-binary dose response curves. Intermediate efficacy readouts tend to be

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less robust as tools for predicting vaccine responses compared to drugs that have specific metabolic effects.

The manufacture of vaccines and drugs are regulated differently, and these differences can play a significant role in the development and commercialization process. Traditionally, regulatory approval of manufacturing processes for vaccines and other biologic products is closely tied to a single manufacturing facility and qualification of additional facilities is more challenging than the case for drugs.⁶

Another practical difference between classic drug and biologic therapeutic products is that currently no comparable “generic drug” approval pathway is available to biologic products.⁷ It has long been contested whether simple peptide products like insulin and growth hormone should be approved under an abbreviated generic (now referred to as biosimilar) pathway. FDA policy is not yet set for even these simple peptide products though the agency appears to be headed toward one. In this respect, FDA has lagged the European Medicines Agency (EMA) in providing a biosimilar pathway—EMA having enacted a guideline in 2004. More complex biologic products are not likely to be afforded this pathway for years to come.

Recent History of T1DM Therapeutic Regulation

Therapeutic targeting of islet autoimmunity has necessarily been limited to people with some remaining β -cell function, essentially those just diagnosed with T1DM within a window as little as a few months. This reality results in the need for clinical trials that are relatively long, difficult to conduct, and are not usually preceded by robust “proof-of-concept” trial data, i.e., studies that are formally powered to yield persuasive results on the primary regulatory efficacy endpoint. These and other challenges inhibited the pharmaceutical industry’s pursuit of T1DM therapies even though T1DM affects several million people in North American and Europe, and the prevalence is growing.^{8,9} More recently, large pharmaceutical companies have entered this general therapeutic area.¹⁰ The larger type 2 diabetes mellitus (T2DM) population has dominated the attention of both FDA and pharmaceutical companies alike. For T2DM drugs, the regulatory efficacy endpoint, Hemoglobin A1c (HbA1c), was validated by landmark trials as predictive of microvascular benefit. The design of T2DM registration trials has become standard though the recent requirement of T2DM drugs to have cardiovascular safety data prior to approval has substantially increased the difficulty for developing T2DM drugs.

When FDA was first presented proposals for investigation of T1DM therapies, it held that HbA1c should also be the primary endpoint for T1DM therapies, which led to alarm in the expert community. Specialists in this field understood that ethical and analytical considerations dictated that trials involving people with T1DM should utilize a treat-to-glycemic-target design. Standard of care insulin therapy could not be withheld from any participant. Since insulin therapy is effective—though hazardous—in achieving glycemic control, HbA1c differences between placebo and active treatment groups would tend to be minimized even if the active therapy were fully effective in halting autoimmune

attack. Glycemic control would therefore be an insensitive measure of the performance of a therapy in reducing autoimmune destruction of islets.

FDA’s position led to an October 2001 workshop of international experts, which was sponsored by the American Diabetes Association (ADA) and co-sponsored by the National Institutes of Health (NIH) and the Juvenile Diabetes Research Foundation (JDRF). The conference concluded that the appropriate primary efficacy outcome for T1DM intervention trials is endogenous insulin secretion as measured by C-peptide levels. This view was equally shared by European participants.

The ADA workshop led to a publication of the consensus in 2003.¹¹ An analysis of Diabetes Control and Complications Trial (DDCT) data was included in the consensus statement. This analysis projected that remaining C-peptide reflected endogenous insulin secretion at study entry (>1 year after diagnosis of T1DM) and was predictive of rates of microvascular complications and glycemic control at long term follow-up. The analysis, though not pre-specified, suggested that even a very small amount of preserved endogenous insulin secretion as reflected by C-peptide levels was associated with improved microvascular and glycemic outcomes irrespective of the intensity of glycemic control. The results of the analysis and the strong international consensus supported a change in the FDA’s view about the primary efficacy endpoint for T1DM clinical trials. The use of C-peptide as a more appropriate primary efficacy endpoint for T1DM therapeutic development is now widely accepted—including in FDA’s draft guidance on diabetes drugs.¹² EMA has since issued a draft guideline that is generally similar to the FDA guidance but has fewer details with respect to T1DM therapies. Finalization of this guideline is expected in January 2011.¹³ Advice given to sponsors by EMA and FDA has appeared to be similar. The only difference among experts in the US and Europe is confined to preferences for the procedures involved in stimulating C-peptide secretion.

Regulatory Perspectives on Clinical Trial Design

While regulatory expectations continue to evolve for T1DM therapies, the converging perspectives of the FDA, EMA and the expert community are summarized below.

Target populations and therapeutic indications. The FDA and EMA both recognize the current unmet clinical need for a new means of preserving remaining endogenous insulin secretion in patients with new-onset T1DM. Both agencies would readily approve safe and effective treatments for the retention and/or restoration of endogenous insulin secretion, as well as agents for the prevention of T1DM; however, there are a number of key considerations regarding the determination of the target populations of such treatments.

Initial pivotal trials involving immunomodulators will generally be limited by regulators to adults and older children; the indicated population would then be defined by the parameters used in the pivotal trials. Following the establishment of safety and efficacy in early trials, additional trials including progressively younger children will be allowed and eventually required.

For the moment, EMA appears to accept younger age children than FDA, but this age gap between authorities has narrowed.

The approved therapeutic indication would initially specify that the treatment is 'for the preservation of remaining endogenous insulin secretion in people with recently diagnosed T1DM'. It is anticipated that some limited mention of the DCCT analysis would be allowed in the drug product label, but no claims could be made for expected clinical outcomes, such as the prevention of complications until actual clinical benefits are demonstrated.

Efficacy endpoints. Stimulated C-peptide response is accepted as the regulatory primary endpoint because it is a direct measure of reducing the hormonal deficiency state of T1DM. Clinical benefits can be expected from preserved endogenous insulin secretion as suggested in the DCCT analysis. C-Peptide is often referred to as a surrogate efficacy outcome, but it is important to understand that C-peptide is simply a more reliable means of measuring insulin secretion than measuring insulin itself. C-peptide therefore is better viewed as a methodological approach for assessing endogenous insulin secretion rather than a surrogate outcome or biomarker. C-peptide levels should be measured under standardized conditions—currently, a mixed meal tolerance test (MMTT) or glucagon stimulation test are commonly used. An international study has compared these two approaches and shown that MMTT has the apparent advantage of stimulating more C-Peptide than the glucagon test.¹⁴

Secondary endpoints and their considerations. HbA1c is the gold standard measure of glycemic control, but it is an insensitive measure of improved beta cell function resulting from an intervention. This is particularly the case in a trial in which near-normal glycemic control is targeted with background insulin therapy. HbA1c should not substantially differ between treatment groups when T1DM participants are striving for good glycemic control. Moreover, a trial that has substantial differences in HbA1c between treatment groups would raise interpretation issues since glycemic control itself may affect residual β -cell function. FDA would require glycemic control to at least not worsen and would hope to see trends toward reduced HbA1c.

Both FDA and EMA raise total daily insulin dose (TDID) as another important efficacy endpoint for T1 therapy studies, but has practical limitations. While TDID is expected to differ between placebo and treatment groups, insulin dose is influenced by multiple factors that change moment to moment (e.g., exercise, type of insulin used, intra-individual insulin pharmacokinetics and dynamics, insulin sensitivity, attentiveness of the person, etc.). Thus, the amount of insulin chosen by a person to be injected in a day is likely to vary more than the actual endogenous insulin secretion. Using TDID as a primary efficacy endpoint would substantially increase number of subjects to adequately power a pivotal trial. In addition, no generally accepted magnitude of effect on insulin dose that could be considered clinically meaningful or predictive of clinical benefits has been established. Insulin dose is therefore generally regarded by experts as a supportive secondary endpoint.

Since insulin therapy is fully effective but hazardous because of high risk of hypoglycemia, reduction of hypoglycemia risk is essentially the ultimate objective of all therapies aimed at

preserving or increasing insulin secretion in people with diabetes. Hypoglycemia is by far the most important barrier to achieving normal glycemic control in people with T1DM. Preservation of endogenous, glucose-sensitive insulin secretion should reduce the rates of serious hypoglycemia associated with insulin therapy and suggested by the DCCT analysis. The FDA views the assessment of treatment effects on rates of hypoglycemia as very important but also recognizes the challenges for assessing this outcome in the relatively short duration of pre-approval clinical trials. Severe hypoglycemia rates are relatively low in the new onset populations currently being evaluated, and a clear benefit on hypoglycemia cannot be expected in the first years following diagnosis of T1DM. In support, the benefit of intensive glycaemic control on rates of hypoglycemia in the DCCT was not seen until after the third year of that trial. Even in the general T1DM population, the event rate of hypoglycemia as rigorously defined in the DCCT is low. Large and fairly long trials would be required to achieve adequate statistical power for hypoglycemia as a primary endpoint. Hypoglycemia can be assessed in various ways that yield high event rates, including the use of continuous glucose monitoring, multiple home glucose monitoring using a standardized instrument and self- and family-reported hypoglycemia, but for now it appears that regulators will continue to rely on the rigorous criteria for hypoglycemia used in the DCCT.

Study duration and durability. FDA and EMA now approve therapies for T2DM based on pivotal trials that are 6 months in duration or greater—longer duration may be required in the future. For T1DM therapies, FDA and EMA will require at least 12 months of controlled trial treatment with indefinite follow-up of the study cohorts. However, concerns about safety and durability of effect may drive trials of longer duration. Durability can be evaluated during the course of the controlled trial and, to some extent, during the unblinded follow-up. The trends towards earlier diagnosis and improving glycemic control among the T1DM population may account for the impression that the decline of insulin secretion is becoming somewhat less steep in the first years following diagnosis. If so, this reduced rate of decline would have the effect of necessitating longer trials to achieve adequate statistical power to show treatment effects.

In evaluating T2DM therapies, FDA to date has not required a formal evaluation of glucose-lowering durability. Indeed, the usual pattern of T2DM therapies is to fail over time. Durability will be a more important question for T1DM therapies aimed at new onset populations because if no difference in insulin secretion is seen between treated and placebo groups several years after diagnosis, the prospects of seeing any longer term clinical benefits are greatly reduced. In the current context of no approved therapies, it appears that evidence for durability, or lack thereof, of a particular T1DM therapy will be taken into the overall benefit to risk assessment. However, FDA and EMA are likely to require some formal assessment of long term durability, if not clinical outcomes, in the post-approval period.

Statistical approaches and effect size. Standard statistical approaches based on C-peptide as a continuous variable are to be used to size the pivotal T1DM trials. Considerable complexity

is involved in the statistical design of T1DM trials.^{15,16} The key unresolved question is what would be regarded by the regulatory authorities as the minimally acceptable treatment effect size at the end of the treatment period—and various points beyond. Given the lack of availability of an approved therapy, it is conceivable that FDA would accept on the order of a 20–30% placebo-adjusted difference in C-peptide secretion. A categorical approach might also be accepted, which could consist of the difference in the proportion of subjects maintaining a C-peptide response above a pre-specified level. Such an approach is used in FDA's evaluation of weight loss therapies.¹⁷

Dose and regimen optimization. T1DM therapies typically are not amenable to robust study of dose relationship to efficacy endpoint response. Likewise dose regimen optimization is also challenging. Use of surrogate immune markers in smaller and shorter clinical trials as well as animal model data may help to support a dose and regimen for one or two selected doses and regimens in pivotal trials. Realistically, because of the relatively large sample sizes required for accessing effects on C-Peptide, decisions on phase 3 trial dose will be based on less data than is usually the case for conventional drug therapies. FDA accepts that reality but will require further assessment of how long a chronic or recurrent therapy should be dosed, continued or repeated. Randomizing trial subjects to various regimens, including no therapy following the completion of the initial treatment period, would provide valuable additional data. This would be done post-initial approval, but a subsequent reliable readout could take an additional two years or longer.

Basis for regulatory approval. In reaching a licensing decision for any therapeutic product, the regulator weighs the observed or likely benefits against the risks suggested by all relevant data. FDA and EMA now understand that some partial preservation of endogenous insulin secretion should result in clinical benefits. The expert community's advice will be sought on what is a minimally acceptable treatment effect and just how minimally durable that effect should be. A minimum clinically meaningful level may be established in the future, but for now the necessary effect size will depend on the specific therapy's safety profile and rough clinical judgment.

Other Considerations

T1DM prevention. Prevention of both forms of diabetes represents one of the major aspirations of public health policy and biomedical research. Some discussion is given to prevention of T1DM and T2DM in the FDA draft guidance on diabetes drugs, but both disease targets are daunting for different reasons. A number of trials with various interventions including dietary-related¹⁸ have been aimed at T1DM prevention, but perhaps most illustrative of the Herculean effort required is the Diabetes Prevention Trial (DPT-1).¹⁹ In order to identify a cohort of sufficient risk for developing T1DM, over 84,000 first-degree and second-degree relatives of patients with diabetes were screened for islet-cell antibodies. Just over 3,000 tested positive and of those about 2,100 went on to genetic, immunologic and metabolic testing to ascertain risk. Then 339 patients were randomized to low

dose subcutaneous insulin or close observation. Conversions to T1DM occurred in 69 and 70 subjects, respectively, over nearly 4 years of follow-up.

The DPT-1 experience and others make clear that T1DM trials aimed at a prevention indication are unlikely in the foreseeable future. The status of diagnostics for identifying high risk patients and the paucity of therapeutic candidates that could be utilized in a prevention trial without any further qualification virtually rule out the pursuit of a prevention claim without first having achieved a treatment indication.

Islet regeneration therapies and combination approaches. Few with T1DM can benefit from immunomodulatory therapy alone since lost β -cell mass does not spontaneously return. Evidence is mounting that progenitor or stem cells reside in the ductal tissue of the pancreas, even after many years of disease and may be induced to differentiate into functional islets.²⁰ Several therapeutic candidates have shown true islet-regenerating activity (not to be confused with agents that improve β -cell function or reduce β -cell apoptosis) in animal models. At least one regeneration therapy is now under clinical development.²¹ Combining a regeneration agent with an immunomodulator offers the prospects of a synergy in restoring islet mass. Promising results have been reported in the NOD mouse model of well-established T1DM using an IL-12 inhibitor, lisofylline²² and an islet-regenerating agent, INGAP (islet neogenesis-associated protein) peptide.²³ When given alone lisofylline resulted in no reduction in hyperglycemia. INGAP alone resulted in only modest reduction of hyperglycemia, although insulin levels increased substantially. When both therapies were given together, insulin levels normalized and hyperglycemia was reversed.²⁴

Such immunomodulatory and regenerative combination approaches not only have the potential for returning endogenous insulin secretion but secretion of other important islet hormones such as glucagon—and in people with established as well as new onset T1DM. Because those with established T1DM start with essentially no endogenous insulin secretion, fewer subjects and less time to detect treatment effects on C-peptide and supportive secondary endpoints will be required. The FDA has well-established principles for developing combination therapies. Generally a toxicology study of the combined therapy is required in addition to the complete package of nonclinical studies required for each individual therapy.²⁵ A clinical study is generally required to demonstrate the contribution of each agent to the combined treatment in a factorial design.²⁶ Despite the clear need for a multifactorial therapeutic approach toward T1DM, large pharmaceutical companies and investors have traditionally shied away from co-development of two combination therapies that are unapproved. This is slowly changing, particularly in areas that have been resistant to monotherapy approaches, obesity being probably the most relevant example.²⁷ An example of a co-developed investigational combination drug product approved by the same FDA division that regulates diabetes products is Mecasermin rinfabate (iPlex, Insmed Inc.). This product consists of insulin-like growth factor (IGF-1) and its plasma binding protein, IGF-binding protein-3 (IGFBP-3).²⁸ The product has since been removed from the market because of patent litigation.

Vaccine paradigm. Many T1DM therapies for T1DM autoimmunity will essentially function as vaccines, not as conventional drugs and the development of vaccines and drugs can differ in substantial ways. As noted above, clear dose-response relationships are not typically seen with vaccines as they are with classical pharmacologic agents. FDA can be expected to apply a mix of drug and vaccine perspectives in evaluating immunomodulatory approaches for both efficacy and safety.

Regulatory provisions. The prevalence of new onset T1DM qualifies for Orphan Drug status at both FDA and EMA. For now, FDA has not granted “Fast Track”²⁹ status for immune therapies aimed at T1DM.

Public health policy and general drug development issues. Drug safety controversies, peaking with Vioxx (rofecoxib) and Avandia (rosiglitazone), have led to much caution at FDA, among large pharmaceutical companies and investors. This is particularly true for metabolic drugs. While these concerns generally center on therapies for large populations, the impact at FDA is to cause greater risk aversion among drug evaluation in general. To some extent, this risk aversion extends even to therapies aimed at clear unmet clinical need, such as those for T1DM. A somewhat related challenge for the pharmaceutical industry is the increasing costs of therapeutic development. Drug development is inherently risky and costly, mainly due to attrition of drug candidates from company pipelines. The cost of producing a single approved new molecular entity is estimated to approach or exceed \$1–2 billion.^{30,31} Though FDA and EMA may accept a somewhat smaller number of total patients in T1DM development programs, the long duration of these trials may lead to total costs that approach those of T2DM drugs. Encouragingly, some T1DM therapeutic programs have attracted major pharmaceutical company involvement,³² but development of all diabetes therapies and T1DM in particular will continue to be challenged by the time, costs and risks involved.

It is clear that immunotherapies will be required to achieve the ultimate goals of both a fully effective treatment and universal

prevention vaccine for T1DM. But, progress towards these goals will only be made in slow, stepwise fashion. The first T1DM therapies will be approved for new onset disease. It is likely that combination of some of these therapies will prove to be more effective than the monotherapies. An approved indication for established T1DM will follow after it is shown that one or more of these immunotherapies in combination with islet regeneration agents, islet transplant therapy or stem cell therapy results in return of islet function. A prevention vaccine for any population will not be feasible until the candidate has first been proved effective as a treatment for new onset and/or established T1DM. Advances in better defining at risk people are also needed to facilitate the development of prevention vaccines. A universal vaccine that would be given to the general population of infants and children will not be possible until years of experience have accumulated with a vaccine approved for an at risk population.

Conclusions

The outlook for new onset T1DM therapeutic development has improved, in part, because of the convergence of regulators’ and clinical development experts’ thinking about how these therapies should be assessed for efficacy. This has led to increased participation of large pharmaceutical companies in the field. A number of key issues remain to be resolved. These will be faced soon since several immunomodulator candidates aimed at new onset T1DM have approached or entered phase 3 clinical trials. Prospects are emerging for immunotherapy treatment of people with established T1DM, a population that far outnumbers those with new onset T1DM. This prospect is contingent on approaches aimed at restoring or replacing islet tissue. Fully effective treatment of both new onset and established T1DM will likely require a combination of two or more therapies, in a sense, similar to therapeutic combinations required for metabolic control of T2DM. Given that T1DM is the result of an autoimmune disorder, immunotherapy will be a key part of any fully effective biologic approach.

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