What Will It Take to Get Therapies Approved for Type 1 Diabetes?

Alexander Fleming

Kinexum, Harper’s Ferry, West Virginia, USA

The development of therapies for T1D has been neglected in favor of efforts in advancing therapies for the larger T2D population. Pharmaceutical companies have also been deterred by lack of clarity around the regulatory expectations for such therapies. The prospects for therapy for new-onset T1D have brightened in some respects because of convergence among regulators and clinical experts in views about how these therapies should be assessed. The most important consensus is that the primary efficacy endpoint for treatments directed at the underlying autoimmune cause of T1D should be endogenous insulin secretion, as reflected by standardized C-peptide measurements. Most T1D therapeutic development efforts are directed at new-onset disease, which represents a small proportion of the entire T1D population. A major deficiency in T1D therapeutic development is the lack of activity in advancing therapies for people with established T1D, a population that far outnumbers those with new-onset disease. Complete remission of new-onset or established T1D will almost certainly require a combination of two or more therapies to address the underlying cause of the disease and restore normal insulin function.

Key words: FDA; T1D; immunomodulatory; regulatory; C-peptide; insulin; hypoglycemia

Introduction

The United States Food and Drug Administration (FDA) and other regulatory authorities have long been in a quandary about how to approve therapies directed at the underlying autoimmune cause of type 1 diabetes (T1D). Therapeutic targeting of islet autoimmunity has been focused to date on persons with some remaining β-cell function, essentially those just diagnosed with T1D. This target population requires reenrolling in a registered clinical trial, which are relatively long and difficult to conduct. These and other challenges have slowed the pharmaceutical industry’s pursuit of T1D therapies, even though it afflicts more than 1 million North Americans. The larger type 2 diabetes (T2D) population has dominated the attention of regulators and pharmaceutical companies alike. For T2D drugs, the regulatory efficacy end point, hemoglobin A1c (HbA1c), was validated by landmark trials as predictive of microvascular benefit, and the design of T2D registration trials has become standard. For some time, the FDA assumed that HbA1c should also be the primary end point for T1D therapies. However, this position caused concern among the expert community. Clinicians and trial designers understood that for ethical and analytical reasons, T1D trials have to consist of a treat-to-glycemic-target design. This design will tend to minimize treatment group differences in HbA1c. Glycemic control would, therefore, be an insensitive measure of expected clinical benefits for clinical trials in T1D.
Recent History

This initial regulatory policy 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). A consensus was reached that the appropriate primary efficacy outcome for T1D intervention trials is endogenous insulin secretion as measured by C-peptide levels. Around this time, the European Agency for the Evaluation of Medicinal Products (EMEA) issued a guideline for T1D and T2D therapies, but it did not address therapies for the underlying cause of T1D. However, sponsors who conferred with European national authorities were generally given advice consistent with the ADA consensus. The publication from the ADA workshop in 2003 containing an analysis of the Diabetes Control and Complications Trial (DCCT) data proved ultimately persuasive to the FDA. This analysis examined the relationship of endogenous insulin secretion at study entry (>1 year after diagnosis of T1D) and rates of microvascular complications and glycemic control at long-term followup. The analysis suggested that a relatively small preservation of endogenous insulin secretion, as reflected by C-peptide levels, is associated with improved microvascular and glycemic outcomes irrespective of the study treatment assignment, including the intensive glycemic control group. The results of the analysis and the expert consensus supported a change in the FDA’s view about the primary efficacy endpoint for T1D clinical trials. Though the analysis of C-peptide data was not prespecified, the use of C-peptide as a more appropriate primary efficacy end point for T1D therapeutic development is now widely accepted.

This article discusses impressions of the converging perspectives of the FDA, EMEA, and the expert community.

Target Populations and Therapeutic Indications

The FDA and EMEA both recognize the current unmet clinical need for a new means of preserving remaining endogenous insulin secretion in patients with new-onset T1D. 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 T1D; 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. After the establishment of safety and efficacy in early trials, additional trials including progressively younger children will be allowed, and eventually required.

Until actual clinical benefits are demonstrated, the therapeutic indication would presumably specify that the treatment is for the preservation of remaining endogenous insulin secretion in people with recently diagnosed T1D. 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.

Study Design

Duration and Durability

The FDA and EMEA now approve therapies for T2D based on pivotal trials that are 6 months in duration or longer. For T1D therapies, it is likely that the FDA 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.

All T1D studies must adhere to accepted standards of care in managing glycemia and co-morbidities. In particular, trial participants should be managed to achieve near-normal glycemic control. Incorporating aggressive glycemic targets in T1D trials will also improve the ability to demonstrate effects on the secondary efficacy outcomes—rates of hypoglycemia and total daily insulin dose.

**Efficacy End Points**

**Primary End Point: Endogenous Insulin Secretion as Reflected by Stimulated C-Peptide Levels**

T1D results in a hormonal deficiency state. Clearly, the appropriate primary basis for assessing the efficacy of a T1D therapy is the extent to which this deficiency state is corrected. As discussed above, clinical benefits can be expected from preserved autoregulated insulin secretion. 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 part of a methodologic approach for assessing endogenous insulin secretion rather than a surrogate outcome or biomarker. Endogenous insulin secretion should be assessed by measurement of C-peptide levels 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 the results are expected soon.\(^5\)

**Secondary End Points and Their Considerations**

HbA1c is a highly valuable clinical measure of glycemic control, but it is an insensitive measure of \(\beta\)-cell function, particularly in a trial in which near-normal glycemic control is sought. In such trials, HbA1c is not expected to substantially differ between treatment groups; in fact, a trial that results in substantial differences in HbA1c between treatment groups would be problematic from the standpoint of interpreting the results since glycemic control conceivably may affect residual \(\beta\)-cell function. Therefore, HbA1c is regarded as an important measure of trial integrity and as a check against adverse effects of the therapy on glycemic control.

Total daily insulin dose is another important efficacy end point, but has significant limitations. The insulin dose is expected to differ between placebo and treatment group. Insulin dose is also influenced by multiple factors (e.g., exercise, type of insulin used, intra-individual insulin pharmacokinetics and dynamics, insulin sensitivity). Thus, this parameter is likely to have more variability than the underlying endogenous insulin secretion. From a biostatistical perspective, it would be challenging to adequately power a trial with a measure of much higher variability than that of the endogenous insulin secretion. 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. Therefore, insulin dose will be seen as a supportive secondary end point.

Hypoglycemia is the most important barrier to achieving normal glycemic control in people with T1D. Preservation of endogenous, glucose-regulated insulin secretion should reduce the rates of serious hypoglycemia associated with insulin therapy. Reduction of hypoglycemia is therefore the *raison d’être* of therapies aimed at the underlying cause of T1D. Accordingly, the FDA views the assessment of treatment effects on rates of hypoglycemia as very important, but is also cognizant of the challenges in assessing this outcome, especially over the relatively short duration of preapproval clinical trials. The event rate of hypoglycemia
as rigorously defined in the DCCT is low, and a clear benefit on hypoglycemia is not expected in the first years after diagnosis of T1D. Likewise, the benefit of intensive glycemic control on rates of hypoglycemia in the DCCT was not seen until after the third year of that study. Hypoglycemia can be assessed in various ways, including the use of continuous glucose monitoring, multiple home glucose monitoring using a standardized instrument, and self- and family-reported hypoglycemia, but regulators will continue to rely on the rigorous criteria established in the DCCT.

**Statistical Approaches and Effect Size**

Standard statistical approaches are to be used to size the pivotal T1D trials and provide prespecified analysis plans. The key unresolved question is what would be regarded by the regulatory authorities as the minimally acceptable treatment effect size. 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 analysis approach might also be accepted. This might consist of the difference in the proportion of subjects maintaining a C-peptide response above a prespecified level.

**Basis for Regulatory Approval**

As is true for the licensing of any therapeutic product, the regulator weighs the observed or likely benefits against the risks suggested by clinical and nonclinical data to reach a decision about approvability and the appropriate drug product label. The FDA and EMEA 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. While such a threshold may become an established standard, the magnitude of benefit that would be required for a particular therapy would depend on that specific therapy’s safety profile.

**Islet Regeneration Therapies and Combination Approaches**

The large majority of persons with T1D cannot expect to benefit from immunomodulatory therapy alone since it does not directly address the almost total loss of β-cell mass, which otherwise occurs within a few weeks of clinical onset. Evidence is building 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, but this remains an area of controversy. A number of therapeutic candidates have shown true islet-regenerating activity (to be distinguished from agents that may induce β-cell replication or reduce β-cell apoptosis) in animal models and at least two are under clinical development. Figure 1 exemplifies the value of combining a therapy that controls the autoimmune destruction of islets with a therapy that induces islet neogenesis. In the NOD mouse model of well-established T1D, an immunomodulatory agent, lisofylline, and an islet-regenerating agent, INGAP (islet neogenesis-associated protein) peptide. 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. Figure 1 shows apparent regeneration of islets as evidenced by insulin and PDX staining resulting from the combined treatment.

Combination therapeutic approaches conceivably can extend the potential for restoration of normal metabolic control by returning not only endogenous insulin secretion, but also secretion of other important islet hormones such as glucagon for all people with T1D.
Figure 1. Regenerated islets with insulin and PDX staining resulting from combined treatment with INGAP and LSF in NOD mice with established T1D. The result of combined islet regeneration and immunomodulatory therapy is demonstrated with immunohistochemical staining for insulin (left panels) and the islet marker, PDX-1 (right panels). NOD mice were started on insulin pellets after three successive measures of plasma glucose exceeding 250 mg%. LSF was then started followed by INGAP peptide treatment. Vehicle- and monotherapy-treated animals showed essentially no clinical response and minimal histologic evidence of new islet formation (data not shown). (Illustration courtesy of Dr. Jerry Nadler, Jeffrey Carter, Sarah Tersey, and Elizabeth Kropf.)

Since those with established T1D start with essentially no endogenous insulin secretion, treatment effects resulting from islet regeneration as measured by C-peptide as well as supportive secondary endpoints will require fewer subjects and less time to detect. 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. At least one clinical study must be conducted that demonstrates in a factorial design the contribution of each agent to the combined treatment effect.

Substantial efforts aimed at developing drug combinations in the T2D therapeutic area are the rule and not the exception. However, large pharmaceutical companies and investors have traditionally shied away from co-development of two combination therapies, one of which has not already been approved. This is no longer the case, particularly in areas that have been resistant to monotherapy approaches, obesity being probably the most relevant example. A recent 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.), which consists of insulin-like growth factor (IGF-1) and its plasma binding protein, IGF-binding protein-3 (IGFBP-3). Availability of robust treatments to people with T1D will be substantially delayed if investigational agents are only developed in isolation and in sequence.
Other Considerations

Mechanism of Action—Vaccine Paradigm

Most T1D therapies for T1D autoimmunity will essentially function as vaccines, not as drugs, and the development of vaccines and drugs differ in substantial ways. For example, clear dose–response relationships are not typically seen with vaccines as they are with classical pharmacologic agents. The FDA can be expected to apply a mix of drug and vaccine perspectives in evaluating immunomodulatory approaches for both efficacy and safety.

Dose and Regimen Optimization

Because T1D therapies will typically not be amenable to exploration of multiple doses and regimens in clinical trials, animal model data may help to support going forward with a single dose and regimen in pivotal trials. The FDA may require some assessment of how long a chronic or recurrent therapy should be continued or repeated. Randomizing trial subjects to various regimens, including no therapy after the completion of the initial treatment period, would provide valuable additional data. Presumably, this portion of the trial would be completed after initial approval.

Durability of Effect

In the case of T2D, durability of effect has not been formally evaluated, though it is clearly an important aspect of a therapy’s performance. Durability, or lack thereof, of a T1D therapy will be taken into the overall benefit-to-risk assessment (see below) made in the initial drug approval process. That is, the FDA does not likely have specific expectations for demonstrating durability; however, the FDA is likely to require some formal assessment of long-term durability, if not clinical outcomes, in the postapproval period.

Regulatory Provisions

New-onset T1D, depending on the definition, qualifies for Orphan Drug status at the FDA and EMEA. It appears that the FDA is not likely to grant “fast track” status routinely for T1D.

Public Health Policy and General Drug Development Issues

Drug safety issues such as those involving Vioxx (rofecoxib) and Avandia (rosiglitazone) have put the FDA under public and Congressional scrutiny. While these concerns generally center on therapies for large populations, the impact at the FDA is to cause greater risk aversion among reviewers. This effect may extend into review of therapeutic efforts aimed at clear unmet clinical need, such as those for T1D. 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 approaches $1 billion. The most costly losses arise from late-stage cancellation of development programs, which arise from unforeseen toxicity issues or from lack of enough clinical benefit to outweigh risks of adverse events. Though the FDA and EMEA may accept a somewhat smaller number of total patients in T1D development programs, the long duration of these trials may lead to total costs that approach those of T2D drugs. Encouragingly, some T1D therapeutic programs have attracted major pharmaceutical company involvement, but development of all diabetes therapies and therapies for T1D in particular will be valued by industry with consideration of these economic and political pressures.

Conclusions

The prospects for new-onset T1D therapeutic development have improved, in part, because of the convergence of regulators’ and clinical development experts’ thinking about how these therapies should be assessed for efficacy. A number of key issues remain to be
resolved. These will be faced soon since several immunomodulatory candidates have approached or entered Phase 3 clinical trials. For persons with established T1D, a population that far outnumbers those with new-onset diabetes, a major deficiency in development efforts remains. Complete remission of all cases of T1D will likely require a combination of two or more therapies, in a sense, similar to therapeutic combinations required for metabolic control of T2D. While challenges remain, noninvasive medical therapies to prevent and reverse autoimmune destruction of islets are no longer vain hopes.

**Acknowledgments**

The material shown in Figure 1 was the result of research funded by the Iacocca, Farish, and Ella Fitzgerald Foundations and by the American Diabetes Association.

**Conflicts of Interest**

Serve as a paid advisor to many companies developing T1 and T2 therapies. I hold a major interest in the development of a islet neogenesis compound.

**References**