From pumps to prevention: recent advances in the treatment of type 1 diabetes

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Treatment options for pediatric patients living with type 1 diabetes mellitus (T1DM) have drastically changed over the past 30 years. Technological advances including the development of continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring (CGM) have allowed for improved insulin delivery and a better understanding of blood glucose fluctuations. Manipulations of CSII and CGM will allow for the development of an artificial pancreas; initial studies of this technology will be reviewed. New medications for the treatment of T1DM have been developed, such as rapid-acting insulins. Another area of exploration is the autoimmune process that causes β-cell destruction. Immunomodulators used for T1DM prevention and secondary intervention will be reviewed.

Introduction

Since the discovery of insulin, treatment of children and adolescents with type 1 diabetes mellitus (T1DM) has been recognized to be especially challenging (Box 1). In this review, we discuss how recent technological advances, such as the development of insulin analogs, improvements of insulin pumps and the introduction of continuous glucose monitors (CGM) have provided pediatric practitioners with important new tools to improve the management of youth with diabetes. We will also discuss the current status of experimental therapies aimed at diabetes prevention and β-cell preservation.

Enhancing insulin delivery: new and improved insulin pumps

Over the past 30 years, advances in diabetes technology have helped to improve the outcomes of management of T1DM. In the late 1970s, methods for self-monitoring of blood glucose and continuous subcutaneous insulin infusion (CSII) pump therapy were introduced. CSII provided a means to achieve near-normal glucose and glycosylated hemoglobin (HbA1c) levels [1,2] but this new therapeutic tool was not widely embraced. Clinicians and patients often feared hypoglycemia more than future complications (such as retinopathy, neuropathy and nephropathy that represent microvascular complications and macrovascular complications like myocardial infarction) and at the time, it was not known that lower HbA1c levels resulted in fewer vascular complications. The large size and difficulties in using early pump models also discouraged their use.

Even after the Diabetes Control Complications Trial (DCCT) showed in 1993 that the benefits achieved from intensive therapy, defined as either multiple daily injections (MDI) or pump therapy, in adolescents and adults with T1DM outweighed the sharp increase in the risk of severe hypoglycemia [3,4], use of CSII in the pediatric age group was limited. It was not until after 2000 that the first reports describing clinical outcomes in children and adolescents who switched from MDI to CSII began to appear [5,6]. As shown in Table 1, a consistent pattern of responses emerged: mean HbA1c fell by $\sim$0.5% [5–19,21], the frequency of clinically important hypoglycemia was reduced [6–13,15–21], and body mass index (BMI) (an index of relative weight calculated from weight divided by height squared) percentiles did not increase thus demonstrating no increased weight gain out of proportion to what would be expected for age in children on pump therapy [6–10,12,14–20]. Of note, studies also showed that switching from glargine, a long-acting basal insulin administered as a once daily injection that is considered to be a gold standard for MDI therapy, to CSII improved glycemic control [11,14], that CSII was efficacious

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BOX 1

Pathogenesis and management of type 1 diabetes mellitus (T1DM)

T1DM is a polygenic, multifactorial autoimmune disease. Pancreatic β cells, which are responsible for the production of insulin, are errantly identified as foreign and are attacked by the immune system in a process mediated through T-lymphocytes. An imbalance between regulatory T cells and pathogenic T cells leads to β-cell destruction. In the fasting state, insulin regulates the production of glucose by the liver and following meals facilitates the entry of glucose into the peripheral tissues. When a crucial mass of pancreatic β cells is destroyed, patients present with hyperglycemia. When the blood glucose is >180 mg/dL, glucose spills into the urine and osmotic diuresis results. When insulin concentrations fall to very low levels, lipolysis increases and ketone bodies are produced in excess, which can lead to diabetic ketoacidosis (DKA).

Once diagnosed with T1DM, patients are initiated on intensive insulin therapy, provided either by multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) therapy. Treatment goals of pediatric patients include near normalization of blood glucose by frequent monitoring, insulin therapy to prevent complications and nutrition sufficient for growth. Hormonal changes associated with puberty lead to relative insulin resistance making control more difficult.

Hemoglobin A1c (HgbA1c) is measured to assess overall glycemic control as it provides a three-month average for blood glucose levels. Normal HgbA1c values range from 4% to 6% (average glucose 68–126 mg/dL), the goal for adult patients with T1DM is targeting a HgbA1c of <7% (average glucose <154 mg/dL). Achieving this glycemic control has been demonstrated to prevent complications; however, the risk of hypoglycemia must be balanced.

in infants, toddlers, and preschoolers [6,12,15,17] and that the beneficial effects of CSII could be sustained for over 3.5 years [12,18,19,22].

Randomized trials that involved children and adolescents have also been completed to assess the efficacy of CSII in comparison to MDI (Table 2). A meta-analysis of such randomized control trials in pediatrics showed that the use of CSII resulted in a significant reduction in HbA1c versus MDI [32]. In those studies that were unable to show a statistically significant difference in HbA1c, other benefits of CSII included improved quality of life and treatment satisfaction [24]. The vast majority of patients who participated in these trials chose to continue on CSII therapy at the conclusion of the studies [32].

More widespread adoption of CSII therapy in pediatrics has also been fueled by improvements in the devices themselves. New features important to children and adolescents include smaller size, the availability of multiple programmable basal rates, the ability to suspend or set a temporary basal rate, the ability to adjust basal and bolus doses accurately in very small increments, availability of a variety of improved infusion sets and the introduction of 'patch pumps'. The delivery of bolus doses has become more precise with the advent of smart pumps that can be programmed with correction factors (or insulin sensitivity factors) and carbohydrate to insulin ratios to calculate bolus dose requirements [33]. By allowing more flexible and precise insulin delivery, patients are able to more closely mimic normal physiologic insulin secretion. The bolus history function allows clinicians and parents to assess whether patients are missing bolus doses of insulin; a feature that is of utmost importance in adolescents [34,35].

The benefits and risks of pump therapy were recently reviewed by a Pediatric Consensus Conference and a position statement made by the Lawson–Wilkins Drug and Therapeutics Committee [36,37]. The consensus conference provided guidelines as to when

TABLE 1

Results of switching from injection to CSII therapy in nonrandomized pediatric studies

Author (reference)	*N*	Age (years)	*Δ* in hemoglobin A1c from baseline % (*P*)	Hypoglycemia	BMI
Boland *et al.* [5]	75	12–20	0.9 (0.02)	Reduced	No change
Ahern *et al.* [6]	161	1–18	0.6–0.7 (<0.02)	Reduced	No change
Maniatis *et al.* [7]	56	7–23	0.2 (0.045)	Reduced	No change
Sulli *et al.* [8]	40	4–25	0.7 (<0.05)	Reduced	No change
Plotnick *et al.* [9]	95	4–18	0.4 (<0.001)	Reduced	No change
Willi *et al.* [10]	51	1–16	0.45 (<0.01)	Reduced	No change
Alemzadeh *et al.* [11]	40	10–18	0.6 (<0.002)	Reduced	Increased
Weinzimer *et al.* [12]	65	1–6	0.6 (0.003)	Reduced	Slight decrease
Mack-Fogg *et al.* [13]	70	2–12	0.5 (<0.0001)	Reduced	Slight increase
Schiaffini *et al.* [14]	20	6–18	0.9 (<0.05)	No change	No change
Jeha *et al.* [15]	10	1–6	0.9 (0.01)	Reduced	No change
Nimri *et al.* [16]	279	1–40	0.51 (<0.01)	Reduced	No change
Behre *et al.* [17]	33	2–7	0.7 (<0.001)	Reduced	No change
Sulli and Shashaj [18]	42	4–17	0.7 (0.00)	Reduced	Reduced
Scrimgeour *et al.* [19]	291	Mean age 13.3	0.4 (<0.0001)	Reduced	No change
Jakisch *et al.* [20]	868	0–18	+0.6	Reduced	No change
Litton *et al.* [21]	9	1–3.5	1.6 (<0.001)	Reduced	No change

TABLE 2

Results of randomized clinical trials comparing CSII and MDI in patients with type 1 DM

Author (reference)	*N*	Age (years)	A1c% (CSII versus MDI)
De Vries *et al.* [23]	79	18–70	8.4 versus 9.2*
Weintrob *et al.* [24]	23	9–14	8.0 versus 8.1.
Hoogma *et al.* [25]	272	18–65	7.4 versus 7.7*
DiMeglio *et al.* [26]	42	<5	8.5 versus 8.7
Wilson *et al.* [27]	19	1–7	7.8 versus 8.1
Fox *et al.* [28]	26	1–6	7.2 versus 7.5
Opipari-Arrigan *et al.* [29]	16	3–6	8.4 versus 8.2
Doyle *et al.* [30]	32	8–21	7.2 versus 8.1*
Schiaffini *et al.* [31]	36	9–18	7.6 versus 8.2*

* $P < 0.05$.

CSII therapy should be considered in children (Box 2). Virtually every child or adolescent with T1DM meets at least one or more criteria for consideration of pump therapy, but candidates should be carefully selected to assure adequate understanding of this therapeutic tool. Several pumps are available and the selection of the pump is based on features desired by the patient/family along with guidance from the multidisciplinary team (Table 3).

Enhancing insulin kinetics and dynamics: rapid and long-acting insulin analogs

Rapid-acting insulin analogs, such as insulin aspart (Novolog® distributed by NovoNordisk), insulin glulisine (Apidra® distributed by Sanofi Aventis) and insulin lispro (Humalog® distributed by Lilly), have a faster onset of action, sharper and earlier peak activity and more rapid return to baseline levels than regular human insulin. More rapid absorption of these analogs also means that much higher peak concentrations of insulin can be achieved in comparison to the same dose of regular insulin.

BOX 2

Indications for use of CSII in pediatrics (adapted from Ref. [37])

Conditions under which CSII should be considered:

1. Recurrent severe hypoglycemia.
2. Wide fluctuations in blood glucose levels regardless of A1c.
3. Suboptimal diabetes control (i.e. A1c exceeds target range for age).
4. Microvascular complications and/or risk factors for macrovascular complications.
5. Good metabolic control but insulin regimen that compromises lifestyle.

Circumstances in which CSII might be beneficial:

1. Young children and especially infants and neonates.
2. Adolescents with eating disorders.
3. Children and adolescents with a pronounced dawn phenomenon.
4. Children with needle phobia.
5. Pregnant adolescents, ideally preconception.
6. Ketosis-prone individuals.
7. Competitive athletes.

The pharmacokinetic and pharmacodynamic advantages of rapid-acting insulin analogs are especially useful in dealing with problems presented by the insulin resistance of puberty [38]. The delayed peak and long duration of action associated with the large bolus doses of regular insulin that are required to overcome the insulin resistance of puberty jeopardize postprandial glucose control in the first two to three hours after eating, and suppress hepatic glucose production five to eight hours later. Given before the evening meal, such large doses of regular insulin increase the risk of nocturnal hypoglycemia. These problems are reduced with rapid-acting insulin analogs [39]. Using the glucose clamp technique to assess the metabolic response to a standard, 0.2 unit/kg bolus of insulin aspart, we have shown that puberty reduces the ability to stimulate glucose uptake but that the absorption of

TABLE 3

Insulin pumps commercially available with corresponding features

Pump	Insulin reservoir capacity (units)	Minimal basal rate increments (U/h)	Minimal bolus dose increments (units)	Other features
Animas Ping	200	0.025	0.05	Smallest pump Largest display screen Meter-remote can wirelessly beam blood glucose and deliver insulin within 10 feet CalorieKing database on meter
Deltec Cozmo	300	0.05	0.05	Integrated freestyle meter Enhanced meal maker® Basal rates by day of week Replacement of basal rate after disconnecting pump
Disetronic Spirit	315	0.1	0.1	Reversible display Menu display customization option
Medtronic Paradigm 522/722	180 or 300	0.05	0.1	Only available pump with real-time CGMS on market Optional remote control for bolus dosing CareLink personal therapy management tool
Insulet Omnipod	200	0.05	0.05	No tubing 1000 common foods in PDA Freestyle meter in PDA component

insulin, the duration of action and the time to peak action are not affected by puberty [40].

The clinical pharmacology of neutral protamine Hagedorn (NPH) insulin poses an important obstacle to safe and effective MDI therapy as there is a considerable dose-to-dose variation in insulin absorption and action [41]. Moreover, because of its maximal effect being seen variably between four and ten hours after administration, this insulin is not ideal for basal insulin replacement, especially during the overnight period. These limitations have been largely overcome by the introduction of the long-acting insulin analogs, detemir (Levemir® distributed by NovoNordisk) and glargine (Lantus® distributed by Sanofi Aventis), the first soluble insulin analogs that have a flat and prolonged time–action profile. Bolus/basal therapy that combines premeal aspart or lispro with glargine or detemir insulin has emerged as the 'gold standard' for intensive injection therapy provided through multiple daily injections (MDI) in adults with T1DM.

A practical disadvantage of MDI with detemir and glargine in youth with T1DM is the large number of injections that are required daily [42]. Unlike insulin suspensions, glargine and detemir cannot be mixed with rapid-acting insulin and must be injected separately. Because basal insulins do not peak, a premium is placed on compliance with injections of rapid-acting insulin before each meal and large snack. Consequently, compliance problems with the frequent daily injections may, in part, explain why randomized pediatric trials have failed to show any advantage of glargine over NPH insulin [43] and inferior performance compared with pump therapy [31].

Enhancing insulin therapy: role of adjunctive therapies

Advances in antidiabetic agents developed primarily for the treatment of type 2 diabetes mellitus (T2DM) might provide adjunctive treatment of T1DM. Metformin, thiazolidinediones (TZD) and glucagon-like peptide 1 (GLP-1) agonists are some of the agents in this group; however, pramlintide is the only drug developed and approved for use in adjunct with insulin therapy for patients with T1DM.

Amylin is a naturally occurring polypeptide hormone that is cosecreted with insulin from β cells. Pramlintide, a synthetic analog of amylin, reduces postprandial hyperglycemia by suppressing glucagon production and delaying the gastric emptying time [44,45]. Clinical studies demonstrated a modest improvement in glycemic control when compared to the placebo group in adult subjects with T1DM without a significant increase in hypoglycemia or weight gain [46,47]. On the contrary, pramlintide use resulted in weight reduction for adults with T1DM, which was probably because of suppression of appetite [47]. Common side effects of pramlintide are nausea, vomiting and the risk of insulin-induced hypoglycemia (http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021332s006lbl.pdf) [48]. Insulin dose with meals are decreased by 20–50% to prevent hypoglycemia as dosage is titrated in 15 mcg increments to a maximum dose of 60 mcg (http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021332s006lbl.pdf). It is FDA approved for ages above 15 and is given by a subcutaneous injection separately from the insulin injection (http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021332s006lbl.pdf).

As in adults, obesity and obesity-related insulin resistance is becoming an increasing problem in youth with T1DM. Metformin is a drug from the biguanide class that decreases hepatic glucose production and increases insulin sensitivity. Its use in adjunctive therapy with insulin has demonstrated better glycemic control (HbA1c improvement of ~0.6–0.9%) than treatment with insulin alone in a few short-term studies conducted in youth with T1DM [49,50]. A randomized, double-blind study with adult patients demonstrated decreased HgbA1c, fasting plasma glucose, and total daily insulin dose in the metformin-treated group in comparison to the placebo-treated group; however, it failed to show any significant change in body weight after metformin was used in addition to insulin [51]. The commonly observed side effect was gastrointestinal discomfort for the metformin-treated group [49–51].

Thiazoladinediones (TZD) provide another means to combat obesity-related insulin resistance by enhancing peripheral glucose utilization because of its effects as an agonist for the peroxisome proliferator-activated receptor-gamma (PPARγ) (http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=7972#section-8.8; http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021073s031lbl.pdf). Activation of the PPAR receptors leads to transcription of insulin-responsive genes and sensitizes peripheral tissues (such as adipose tissue, skeletal muscle and the liver) to the effects of insulin (http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=7972#section-8.8; http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021073s031lbl.pdf). A drug from this group, rosiglitazone, has been shown to improve glycemic control when used in addition to insulin therapy for adults with T1DM when compared to an insulin and placebo-treated group. The groups did not differ in their amount of weight gain and episodes of hypoglycemia [52]. No such effect was demonstrated in adolescents with T1DM when treated with pioglitazone in addition to insulin [53]. Moreover, the pioglitazone-treated group had a statistically significant BMI–*z*-score (an index of relative weight change) increase without a difference in the lipid profile [53]. Edema, weight gain, possible decrease in osteoblastogenesis resulting in reduced bone formation and increased cardiovascular risk with rosiglitazone have been reported as some of the adverse effects of these medications for patients with T2D [54–56] raising serious questions regarding their off-label use in children with T1DM.

GLP-1 belongs to a group of incretin hormones and is released from the L cells of the distal small bowel. It suppresses glucagon, stimulates insulin secretion and has a glucose-dependent insulin sensitizing function. It inhibits postprandial gastric emptying and acid secretion but its biological half-life is very short [57]. Exenatide is a commercially available potent long-acting agonist of the GLP-1 receptor whose *in vivo* effects are similar to GLP-1 resulting in decreased postprandial hyperglycemia [57]. Only a few studies demonstrated an improvement of postprandial hyperglycemia by the slowing of gastric emptying and lowering plasma glucagon levels when GLP-1 agonist is administered before meals for subjects with T1DM [57–59]. Common side effects include nausea and diarrhea. Necrotizing and hemorrhagic pancreatitis have been reported with exenatide and it has not received FDA approval for use in adjunctive therapy with insulin [58]. GLP-1 agonists are also under assessment for use in the proliferation and prolongation of β cell survival (see below) [60].

Enhancing diabetes monitoring: new continuous glucose sensors

While CSII therapy has drastically altered the ability to replace insulin more physiologically, new technology has been introduced to measure glucose levels continuously. Self-monitoring of blood glucose (SMBG) using standard meter methods gives a brief 'snapshot' as to where the blood glucose lies at the time of the test. In comparison, continuous glucose monitoring (CGM) provides streaming 'videos' of data on which changes can be made on a continual basis or in a retrospective assessment of glycemic control.

The original CGM system (CGMS®, MiniMed, Inc., Northridge, CA) was limited to retrospective review of recorded data. While this 'Holter monitor' like approach has had limited use for routine care in pediatric patients, we used the system to show that even youths with average HbA1c levels of 7.7% have exaggerated fluctuations in glucose levels after most meals and asymptomatic hypoglycemia (defined as glucose <60 mg/dL) during many nights [61]. The GlucoWatch G2 Biographer, originally produced by Cygmus, Inc. in Redwood City, CA, who sold the rights to Animas, was the first real-time continuous glucose monitor (RT-CGM) introduced. Unfortunately, this device was not popular because it was difficult to use, caused skin irritation and gave inaccurate readings leading to excessive false alarms for hyper and hypoglycemia [62].

The current generation of RT-CGM devices manufactured by DexCom, Medtronic, and Abbot are more accurate and user friendly than the first generation of CGM systems [63–66]. All three systems require insertion of electrochemical sensors into the subcutaneous tissue where a glucose oxidase reaction allows for the measurement of the interstitial fluid glucose, this measurement is then converted to allow for comparison to capillary blood glucose readings. To assess the utility of CGM in those over age 8, a randomized trial with 322 subjects was recently completed. In this study subjects were randomized to sensor use or standard care with SMBG. The benefits of RT-CGM were identified in the subset of patients 25 years of age or older as the mean HbA1c difference was −0.53% ($P < 0.001$) with no increase in rates of severe hypoglycemia [67]. It is noteworthy that 83% of subjects in this age group used the sensor six to seven days a week for the entire six months of the study. While neither of the two younger subsets of subjects (age 8–14 and 14–25) demonstrated significant between group differences in the change in HbA1c, patients between 8 and 24 years of age who used the sensor six to seven days a week also had a 0.5% or greater drop in A1c values [67].

Although RT-CGM is a useful tool to help improve metabolic control, no system of insulin replacement in type 1 diabetes will be optimal until there is feedback control of insulin delivery on a minute to minute basis. Investigators at several centers are already taking the first step toward the development of an artificial pancreas by combining insulin pump and RT-CGM technology. In an inpatient clinical research center study of ten patients using a completely automated insulin delivery system, the amount of time that blood glucose was between 70 and 180 mg/dL rose from 63% to 75% [68]. While improvement in glycemic control was noted, exaggerated postprandial glycemic excursions remained a problem owing to delays in the absorption of insulin from the subcutaneous infusion site. This led us to hypothesize that a priming bolus of insulin before meals could aid in preventing this meal related hyperglycemia. When this approach was tested, peak postprandial glucose levels were significantly lower in patients on the hybrid system and 82% of all glucose values were within the target range of 70–180 mg/dL [69]. Several investigator groups are currently engaged in the efforts to make the dream of an artificial pancreas a reality.

Halting disease: prevention studies in T1DM

T1DM is a chronic autoimmune disease, which is present years before clinical presentation and involves the progressive loss of insulin secretion that continues after the diagnosis is established [70,71]. Immunologic approaches aimed at preserving endogenous insulin production were recently employed and currently being tested against two target populations: those who have not yet formally been diagnosed with T1DM (prevention studies) and those who have recently been diagnosed (secondary intervention studies). Prevention trials involve subjects who are identified as being at high risk for T1DM through screening of autoantibodies to insulin (IAA), glutamic acid decarboxylase (GAD_{65}), tyrosine phosphatases IA-2 (or ICA 512) and IA-2β and the demonstration of early β-cell dysfunction [72,73]. The European Nicotinamide Diabetes Intervention Trial (ENDIT) was a double-blind placebo-controlled trial performed to establish whether nicotinamide, a component of vitamin B3, could delay or prevent the development of diabetes in high-risk individuals [74,75]. Unfortunately, the rates of diabetes diagnosis did not differ between the two treatment groups.

On the basis of small human trials and rodent studies, the use of insulin to prevent the development of diabetes was explored. In the Diabetes Prevention Trial-1 (DPT-1) study, two methods of prevention were assessed: parenteral insulin in those with a >50% five-year risk of developing T1DM and oral insulin in those with a 25–50% five-year risk of developing overt diabetes (http://www.diabetestrialnet.org) [77]. In the parenteral insulin study, patients were randomized to receive either low-dose, subcutaneous ultralente insulin administered twice daily (total daily dose 0.25 units/kg) and four day intravenous insulin infusion annually or close observation. This intervention did not alter the progression to overt diabetes with about 15% of both groups developing diabetes [76]. Participants assigned to the oral insulin trial were either given 7.5 mg oral insulin or placebo [77]; no prevention or delay in developing overt diabetes was noted in either group. However, in *post hoc* analysis some beneficial effect was seen in the subgroup with IAA >80 nU/mL. A study being conducted by the Type 1 Diabetes TrialNet on the effects of oral insulin only in subjects who have higher IAA is underway (http://www.diabetes-trialnet.org).

A recently completed randomized, controlled trial conducted in Finland showed no benefit of nasal insulin as compared to placebo in children found to be at risk of diabetes development [78]. Despite the disappointing outcomes of these trials, it was determined that studies requiring screening of many individuals to identify potential study subjects and involving prevention are feasible. Several other prevention studies (shown in Table 4) are currently in progress. The Juvenile Diabetes Research Foundation website (www.jdrf.org) provides an excellent resource to search for current clinical trials in T1DM.

TABLE 4

Type 1 diabetes mellitus prevention trials currently being conducted

Agent	Study design	Reference/trial ID
Vitamin D3	Randomized, open-label pilot	NCT00141986
Oral insulin trial	Randomized placebo-controlled, double-blind	NCT00419562
Docosahexaenoic acid (Nutritional Intervention to Prevent Diabetes)	Randomized, placebo-controlled, double-blind pilot study	NCT00333554
Trial to Reduce IDDM in Genetically at Risk (TRIGR)	Test whether delayed exposure to intact food proteins will reduce the changes of developing T1DM	NCT0017977

TABLE 5

Type 1 Diabetes mellitus intervention trials currently being conducted

Agent	Study design	Trial ID
Anti-CD3 (ABATE)	Randomized, open-label	NCT00129259 (http://www.immunetolerance.org)
Thymoglobulin (START)	Randomized, double-blind placebo control	NCT00515099 (http://www.immunetolerance.org)
IL-2 and Sirolimus	Open-label, uncontrolled group assignment to assess safety of regimen	NCT00525889 (http://www.immunetolerance.org)
CTLA-4 Ig (Abatacept)	Randomized, double-blind placebo control	NCT00505375 (http://www.diabetestrialnet.org)
GAD	Randomized, double-blind placebo control	NCT00529399 (http://www.diabetestrialnet.org)
The Rituximab study (anti-CD20)	Randomized, double-blind placebo control	NCT00279305 (http://www.diabetestrialnet.org)
The MMF/DZB study	Randomized, double-blind placebo control	NCT00100178 (http://www.diabetestrialnet.org)
BCG	Randomized, double-blind placebo control	NCT00607230

Halting the destruction of β cells: T1DM secondary intervention studies

Secondary intervention studies are conducted in patients with recently diagnosed T1DM. Early immunologic approaches included the use of chronic immune suppressants, such as cyclosporine, prednisone and azathioprine. However, these drugs had serious side effects, required continuous treatment and decreased in efficacy over time [79,80]. Therapies currently being studied to alter disease progression include antigen nonspecific therapies, antigen-specific therapies and combinations of two agents (two antigen nonspecific therapies, two antigen-specific therapies, or the combination of an antigen-specific and an antigen nonspecific therapy. Many of the therapies used for immunomodulation target suppression of β-cell autoimmunity by either directly or indirectly targeting T-lymphocytes, as the T-lymphocytes are thought to mediate the disease process.

New antigen nonspecific therapies that have the goal of inducing immune tolerance by eliminating self-reactivity so that chronic immune suppression is not required are currently being studied. Intravenous infusions of non-Fc-receptor-binding anti-CD3 monoclonal antibodies have been shown to prevent the loss of insulin secretion in the first two years after diagnosis of T1DM [81–83]. Interestingly, T-cell depletion was not the sole factor in these findings, because circulating lymphocyte counts return to normal by two weeks after the last dose of monoclonal antibody in most patients [81,83]. A transient syndrome similar to acute mononucleosis was noted in 75% of the subjects in the drug-treated group in the trial of anti-CD3 by Keymeulen and colleagues; however, symptoms resolved within two weeks of their appearance and laboratory abnormalities normalized by 12 weeks after treatment [82]. Various other non-antigen-specific immunosuppressants/immunomodulators are also being tested (Table 5).

The DPT-1 parenteral and oral insulin prevention trials fall into the class of antigen-specific interventions. These agents need to be given early in the course of the disease, as epitope spreading could lead to the propagation of disease pathogenesis [84]. In a randomized, controlled trial of 70 patients recruited within 18 months after diagnosis with T1DM, those who were treated within six months after diagnosis of T1DM with 65-kDa isoform of GAD showed higher fasting C-peptide and stimulated C-peptide at the 30 month study endpoint [85]. The trial used alum-formulated GAD, with the use of aluminum adjuvant inducing a humoral rather than a cellular response that is thought to minimize the possibility of β-cell destruction if a cellular response was stimulated instead. A TrialNet study to administer GAD protein to those newly diagnosed with T1DM is planned (http://www.diabetestrialnet.org).

Combination therapies involving more than one agent might be the most useful approach to immune modulation. For example, in nonobese diabetic (NOD) mice models, the use of anti-CD3 therapy coupled with intranasal insulin was more beneficial in reversing the disease than use of monotherapy with anti-CD3 or the antigen-specific therapy alone [86]. The use of two systemic immunosuppressant agents, mycophenolate mofetil (MMF) and daclizumab (DZB) is currently being studied by TrialNet (http://www.diabetestrialnet.org).

An alternative approach is to use agents that promote β-cell regeneration in combination with immune modulation. Following administration of anti-CD3 in NOD mice, the use of exendin-4, an incretin mimetic, led to increased insulin content of residual β cells and in some studies such agents can stimulate β-cell replication [87,88]. Clinical trials to assess the safety and efficacy of this combination of therapies in humans are being planned.

Conclusion

Following isolation of insulin and its application for the treatment of patients with T1DM, it was felt that a cure for T1DM had been devised. While survival of patients with T1DM was prolonged the development of complications arose. From improved insulins to the development of pumps and continuous glucose monitors to intervention and prevention trials to halt disease progression, the past quarter century has seen advances that have allowed for improved glycemic control, decreased rates of complications and improved quality of life for patients living with T1DM. However, the need for constant vigilance on the part of the patient and their family cannot be overlooked as a major contributor to achieving glycemic control. As technological advances continue the refinement of the closed loop system, allowing for integration between a continuous glucose sensor and an insulin pump that can be used in the outpatient setting, will allow for the dream of an artificial pancreas to become a reality. Similarly, as an understanding of the events leading to the development of T1DM and immunomodulators targeted at preserving endogenous insulin production are elucidated it is possible that in the future T1DM can join the ranks of diseases that medical advances have conquered.

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