β-Cell Protection and Therapy for Latent Autoimmune Diabetes in Adults

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Latent autoimmune diabetes in adults (LADA) is a term used to describe a form of autoimmune diabetes that resembles type 1 diabetes, but has a later onset and slower progression toward an absolute insulin requirement. Controversies have been surrounding this concept and several attempts have been made to better characterize and classify it. But LADA still remains poorly understood and defined (1). It was even debated whether LADA exists as a distinct disease entity or it just represents the end of a wide spectrum of heterogeneous immune-mediated diabetes (2,3). Uncertainties concern almost all aspects of this disease, including the nomenclature, diagnostic criteria, epidemiology, natural history, and pathogenesis with genetic, metabolical, and immunological aspects. As a consequence, there is no clear management strategy for it, in terms of therapy and prevention. An ideal therapeutic approach would aim not only at obtaining a good metabolic control, but also at protecting residual β-cell mass and function. Even though ~10% of adults with presumed type 2 diabetes at diagnosis in fact have LADA, only a few studies so far have evaluated therapeutic interventions for LADA, using a hypoglycemic or an immunomodulatory agent.

DEFINITION AND DIAGNOSTIC CRITERIA

Obviously, an important impediment in establishing adequate and effective management strategies is the lack of a good understanding of the disease development and of a clear definition. Difficulties reside from the fact that LADA has features of an autoimmune disease (mainly presence of autoantibodies at onset), with many genetic, immune, and metabolic features of type 1 diabetes, but also shares some clinical, anthropometric, and metabolic traits with type 2 diabetes (Table 1) (2,4). As a matter of fact, LADA was first identified in a subset of phenotypic type 2 diabetes individuals who were positive for islet cells antibodies (ICAs), failed sulfonylurea therapy, and needed insulin replacement earlier than the ICA-negative patients, a finding subsequently confirmed by other groups (5,6).

Various studies have used different inclusion criteria and markers for disease definition, and thus drawing conclusions is difficult (6,7). In the attempt to standardize the diagnosis of LADA, three criteria are currently recommended, but all of them have some pitfalls: criteria 1 and 3 are not categorical traits and are highly dependent on physicians' decisions, and criterion 2 is not specific for LADA (1).

Criterion 1: adult age at onset

Various cutoff ages have arbitrarily been used (between 25 and 45 years), but the proposed lower limit is now 30 years of age (6,7). Nevertheless, since adulthood starts earlier in life, this limit might not be all inclusive.

Criterion 2: presence of circulating islet autoantibodies (at least one)

Because autoantibodies to insulin (IAA) and tyrosine phosphatase-like insulinoma-associated protein 2 (IA2) have been reported to be rather infrequent, the diagnosis basically relies on identifying glutamic acid decarboxylase autoantibodies (GADAs), which is the best single marker for screening. Epitope specificity, antibody levels, and concomitant presence of ICAs discriminate two subcategories of LADA with a different risk toward insulin dependency (8). Obviously, to ascertain an accurate immune profile of LADA, further investigations should be performed.

Criterion 3: lack of insulin requirement for at least 6 months after diagnosis

This criterion is used to distinguish LADA patients from those with type 1 diabetes, but reports indicate that there is a high bias in the time to insulin treatment initiation and it does not depend on disease process, but rather on physicians' clinical judgment (9). In addition, the natural history of the disease, the timing of the diagnosis in relation to it, as well as clinical features at diagnosis (e.g., presence or absence of symptoms) are factors that influence the period of insulin independence (1).

Even though the question regarding pathogenesis of LADA is still not fully answered, it is clear now that there are strong genetic and immunologic similarities to type 1 diabetes, implying that LADA is an autoimmune disease. The differences between the two forms may be due to genetic factors (e.g., presence of protective HLA alleles in LADA) and/or due to qualitative/quantitative dissimilarities in the interaction with environment. It is possible that in the disease course there are differences in the antigenic repertoire triggering immune responses, frequency of autoreactive immune cells, and/or the degree of immune regulation, but these aspects still need to be investigated.

Regarding screening for LADA, no definite recommendations can be done at this time because of lack of enough evidence coming from clinical trials (e.g., no cost-benefit assessment has been performed). A possible algorithm for identifying subjects with LADA is suggested elsewhere (2).

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Table 1—*Clinical and paraclinical features of LADA in comparison to type 1 and type 2 diabetes*

	Age at onset	HLA susceptibility	Autoimmunity (autoantibodies)	Ketosis	BMI	Insulin secretion	Metabolic syndrome	Insulin resistance	Initial therapy
Type 1 diabetes	Young/ adult	Yes (strong)	Yes (strong)	Present	Normal	Absent/low	Infrequent	Absent/ infrequent	Insulin
LADA	Adult	Yes	Yes (by definition)	Absent	Normal/ high	Present (but declines)	Variable	Variable	Insulin/OHA*
Type 2 diabetes	Adult	No	No	Absent	High	Present	Frequent	Present	LSO/OHA

LSO, lifestyle optimization; OHA, oral hypoglycemic agents. *Preferable that sulfonylureas are not chosen as first-line therapy.

It is worthwhile to mention that recent studies have proved that GADA titers have a bimodal distribution in LADA and identify two subgroups of patients with distinct clinical, autoimmune, and genetic features: the one with high GADA titers tended to be younger and leaner and had a lower prevalence of metabolic syndrome and its components, with more prominent traits of insulin deficiency (lower C-peptide, higher A1C) and a profile of more severe/extended autoimmunity (higher prevalence of other diabetes specific [IA-2, ICAs] or other autoimmune disease [thyroid peroxidase] autoantibodies) than individuals with lower GADA titers (10). This finding is indicative of the heterogeneity existing within LADA: subjects with multiple and high autoantibody titers resemble those with type 1 diabetes in various features, whereas individuals with single and low autoantibodies titers resemble those with type 2 diabetes (4,10). It might also have therapeutic implications, since different approaches may be applied to the two groups.

THERAPEUTIC INTERVENTIONS

— Studies have identified that ~10% of adults with presumed type 2 diabetes at diagnosis have markers of islet autoimmunity and become insulin dependent sooner (6). This category might therefore benefit from therapeutic interventions that are different from those for type 2 diabetes and somehow tailored to this condition.

While being safe and practical for everyday use, any potential therapeutic approach for LADA should not only aim at obtaining good metabolic control, but also allow better preservation of the residual β-cell function, since it has been proven that maintenance of even some endogenous insulin production is associated with improved metabolic control and better long-term disease outcome (11). The key question is which drug (or combination of drugs) is most effective in obtaining these goals. Unfortunately, there is no established therapeutic intervention for patients with LADA so far, and they are currently treated as patients with type 2 diabetes.

Obviously, a critical issue is evaluation of β-cell mass and function in response to treatment. A significant limitation of interventional trials in humans is that there are no "gold standard" methods to directly measure β-cell mass in vivo. Newer imaging techniques like positron emission tomography, magnetic resonance imaging, scintigraphy, or neurofunctional imaging approach are undergoing development as noninvasive methods of β-cell mass measurement (12). In the meantime, metabolic tests have been routinely used as surrogate markers, and studies have shown that acute insulin response to arginine, glucose and glucose-potentiated, and arginine-induced insulin secretion can be used as robust tests for estimation of β-cell mass (13). A well-validated and practical means of quantifying insulin secretion in vivo is measurement of C-peptide levels under standardized conditions, which has low variability and high reproducibility, making it a good and reliable marker. In fact, the recommendation of an expert panel convened by the American Diabetes Association was that C-peptide response (CPR) is the most appropriate measure of function and clinical end point of intervention in human clinical trials (14).

Although there is a good proportion of patients with LADA, surprisingly, there are only a few studies that have evaluated interventions for this group, and several others are ongoing (15).

Hypoglycemic agents

Sulfonylureas. Sulfonylureas are commonly used for the treatment of type 2 diabetes and act by stimulating insulin release from the pancreatic β-cells to lower blood glucose levels. The insulin secretion is triggered by binding of sulfonylureas to a specific site on the ATP-sensitive K^+ channels at the level of plasma membrane, which leads to their closure and subsequent opening of the calcium channels and activation of an effector system of insulin release (16). Despite their initial efficacy, there is a progressive reduction in insulin-producing capacity of pancreatic β-cells and deterioration of glycemic control over time. The cause might be exhaustion or desensitization of β-cells by prolonged exposure to sulfonylureas and possibly acceleration of oxidative stress and apoptosis (17). It has also been suggested that stimulation of insulin release might be associated with increased autoantigen expression, which could be deleterious in LADA because it might accentuate the ongoing autoimmune process (2,18). These results suggest that therapy with sulfonylureas in LADA would actually expedite the progression toward β-cells depletion and the necessity of insulin initiation, and several studies have confirmed this hypothesis (19–23).

One medium-term (12 months) randomized control trial (RCT) compared insulin with sulfonylureas (glibenclamide) plus insulin treatment, by evaluating metabolic control (fasting blood glucose [FBG]), insulin secretion (fasting C-peptide [FCP]) and markers of autoimmunity (ICA and GADA) at baseline and at the end of study (20). After 1 year of treatment, the group receiving insulin alone had better metabolic control than the sulfonylureas plus insulin group and had also improved the markers of autoim-

munity (six of eight patients became ICA negative). No differences were found in FCP between groups. Similarly, a study examining the effect of adding insulin to sulfonylureas (glibenclamide) and of withdrawal of sulfonylureas on glycemic control in type 2 diabetic patients seemed to support the exclusion of sulfonylureas in autoantibody-positive subjects, who were less likely to respond to it (19).

A long-term (10 years) three-armed RCT compared conventional treatment (primarily with diet) to sulfonylureas and to insulin (for patients with FBG between 6 and 14.9 mmol/l at baseline) and to sulfonylureas with insulin (for patients with FBG >15 mmol/l at baseline) (21). A total of 60% of the autoantibody-positive patients with FBG >15 mmol/l treated with sulfonylureas progressed to insulin requirement within 2 years (compared with 15% of the autoantibody-negative patients). Similarly, in individuals with FBG of 6.0–14.9 mmol/l, the autoantibody-positive group became more rapidly insulin requiring than the autoantibody-negative group (and the highest proportion was from the autoantibody-positive group allocated to sulfonylurea therapy). This again suggests that the use of sulfonylureas may accelerate insulin requirement when compared with conventional intervention.

Two RCTs conducted in Japan compared sulfonylureas (glibenclamide) with insulin treatment in LADA patients. The first study included ICA^+ subjects and reported that two of five patients treated with sulfonylureas required insulin treatment within 24 months due to failure of treatment with secondary oral hypoglycemic agents (22). At the end of study (30 months), the sulfonylureas group had a worsening of metabolic control and showed a progressive deterioration of β-cell function (during the study period serum stimulated CPR [after an oral glucose tolerance test] decreased with almost 40% from baseline). The second study (the Tokyo study, which included $GADA^+$ subjects) had used as primary outcome an integrated value of serum CRP to a 75-g oral glucose tolerance test (ΣCPR = sum of CPR at 0, 30, 60, 90, and 120 min) and defined insulin-dependent stage as ΣCPR <4.0 ng/ml (23). Similar to the previous trial, this study reported that the group receiving sulfonylurea therapy progressed in greater proportion to the insulin-dependent stage during 57 months of follow-up. The same trends were seen in subgroups of patients that had a preserved CPR and had high GADA titers at baseline. The high GADA titers subgroup treated with sulfonylureas had the greatest proportion of patients progressing to insulin dependency. Moreover, ΣCPR decreased significantly in the sulfonylureas group over 5 years, whereas the same parameter remained unchanged in the insulin group.

Even though it is difficult to generalize these data because the studies had different selection criteria and ethnicity as well as different outcome parameters and follow-up durations, taken together, they do suggest that sulfonylureas accelerate (or at least do not protect against) progressive β-cell failure and are similar to (or worse than) insulin in obtaining good metabolic control. Therefore, sulfonylureas should not be used as first-line therapy in patients with LADA.

Insulin. It would probably seem somehow paradoxical to initiate early insulin treatment in LADA, since this disease is defined by lack of insulin requirement at onset and the therapeutic aim is alteration of the risk of progression toward insulin dependency. The rationale for early insulin intervention though would be improving glycemic control while protecting β-cell function. The exact mechanisms for the apparent beneficial effects of insulin treatment reported in several studies are not yet fully understood, but it is thought that administration of exogenous insulin would allow β-cell rest, at least in part by downregulating the β-cell metabolism and/or by releasing them from the hyperglycemic stress (24). The consequence is a decrease in the severity of insulitis and in the number of infiltrative antigen-presenting cells in and around the pancreatic islets (25). A number of experiments suggested that active β-cells, producing high amounts of insulin, are more susceptible to immune-mediated killing and are also associated with higher antigen expression (18,26). Thus, a reduction of β-cell function and of inflammatory processes in the islets would lead to decreased antigen expression on β-cells and subsequent reduction of T-cell responses (27). Other possible explanations would be that exposure to exogenous insulin would actually promote Th2 immunity in humans, as indicated by an increase in IgG1 and IgG4-IA (antibodies to insulin) (although no secondary spreading to other autoantigens) and induce an activation of insulin-specific regulatory T-cells (Tregs) (28,29). Finally, as insulin is a major autoantigen in diabetes (mainly in type 1A), it is thought that immunization with exogenous insulin would determine immune modulation possibly by tolerance induction or "bystander" suppression of autoreactive T-cells through the local release of regulatory cytokines (27). Nevertheless, it should be noted that parenteral insulin failed to prevent the onset of diabetes in high-risk relatives of patients with type 1 diabetes in the Diabetes Prevention Trial-1, and only oral insulin delayed diabetes onset in a subgroup of individuals with high titers of autoantibodies to insulin. This could imply that the timing and specificity of intervention, selection of adequate candidates, or other (poorer defined) aspects of the immune response are critical for the success of intervention (30).

Some of the above-mentioned studies conducted in LADA patients have shown that insulin treatment is associated with better outcome in terms of metabolic control, insulin secretion, and autoimmune responses against pancreatic β-cells. In two studies, patients receiving insulin monotherapy had improved markers of autoimmunity (six of eight patients in one and four of five patients in the other became ICA negative) (20,22). Glycemic control was significantly improved with insulin monotherapy (after exclusion of sulfonylureas) in the 12-month Cuban study, as evaluated by FBG (20). In the first Japanese trial, the 2-h blood glucose level during the 100-g oral glucose tolerance test tended to decrease from the baseline values, but the A1C remained unchanged 30 months later (22). Importantly, the insulin-treated group had an increased stimulated CPR at 30 months (with >60% from baseline) (22). The second Japanese study showed maintenance of the serum ΣCPR over 5 years (23). Moreover, subgroup analysis suggested that patients with high GADA titers and preserved CPR at baseline were less likely to progress to the insulin-dependent stage with early administration of small doses of insulin.

Overall, these results are encouraging because they imply that the insulin-treated patients maintain better β-cell function. The optimal insulin regimen is not clear. Given that the loss of rapid insulin release occurs early in LADA, replacement with fast-acting insulin might be beneficial. However, from a practical point of view, it might be difficult to initiate multiple insulin injection therapy in LADA patients, especially if their blood

glucose levels are moderately increased. Thus, a long-acting insulin injection might be a good alternative.

Insulin sensitizers (metformin, thiazolidinediones). Because (at least some) patients with LADA have features of metabolic syndrome and a certain degree of insulin resistance, they might benefit from therapy with an insulin-sensitizing drug that improves the peripheral action of insulin and thus indirectly protects β-cells from continuous hyperstimulation of its release.

The specific role of metformin in LADA is not known, since there are no studies evaluating it in this specific group of patients. In addition, a potential risk associated with its use is occurrence of lactic acidosis in patients that progress toward insulin dependency (2).

The thiazolidinediones (TZDs) are in turn a more appealing therapeutic approach because, apart from their effect on glucose homeostasis and lipid metabolism (through peroxisome proliferator–activated receptor-γ), there is evidence that they have other potential beneficial effects on islet β-cells (17). It has been shown that TZDs improve insulin content and secretion, preserve β-cell mass and islet structure, have anti-inflammatory effects, protect β-cells from oxidative stress and apoptosis, and even facilitate β-cell proliferation (31,32). Data from animal models suggest that TZD administration has favorable effects on preservation and augmentation of β-cell mass through a combination of enhanced proliferation and decreased apoptosis (32,33). This effect might be due to regulation of genes controlling proliferation, growth, and differentiation and involve the key β-cell regulatory transcription factor pancreatic and duodenal homeobox 1 (Pdx1) (33,34). This might be significant for the clinical management of LADA in therapeutic efforts aimed at β-cell protection.

A recent RCT compared rosiglitazone plus insulin with insulin alone in LADA patients over a total follow-up period of 18 months (35). Results of 17 patients at 12 months showed no significant change in A1C in the insulin group and a significant decrease from baseline in the rosiglitazone plus insulin group, but at 18 months, this improvement in glycemic control was no longer seen. β-Cell function was evaluated by measurement of FCP, by CPR after a 75-g load, and by the difference between the two (ΔCP = CPR − FCP). At 18 months, the insulin alone group had a significant decrease of the FCP, CPR, and ΔCP compared with baseline, while all of the parameters were maintained in the rosiglitazone plus insulin group. Even though rosiglitazone plus insulin did not improve metabolic control significantly more than insulin alone, it appeared to have a beneficial effect in terms of maintaining C-peptide levels (especially stimulated C-peptide) in the long term. The impact of rosiglitazone alone was not assessed in this pilot study, but the results suggest that it would be worthy to further evaluate the benefit of using TZDs in patients with LADA.

Incretins. Incretin mimetics are a new class of pharmacologic agents developed to improve metabolic control in patients with type 2 diabetes. The most advanced drug of this class is exendin-4, which acts as a full agonist at the glucagon-like peptide (GLP)-1 receptor and has glucoregulatory actions similar to the incretin hormones (glucose-dependent enhancement of insulin secretion and inhibition of glucagon secretion), as well as slows gastric emptying and reduces food intake (36). In addition, exendin-4 has been shown in vitro and in animal models to have trophic effects on the pancreas, since it modifies the susceptibility to apoptotic injury and stimulates β-cell proliferation and islet neogenesis from precursor cells (37). Like the TZDs, exendin-4 has islet growth-promoting effects through regulation of genes controlling proliferation, growth, and differentiation, apparently by targeting different components of the epigenetic machinery (34). It induces multiple signaling pathways intrinsic to β-cells (including expression of Pdx-1), which results in expansion of β-cell mass through promoting differentiation of precursor into mature β-cells and stimulation of mature β-cell proliferation (38,39). Therefore, the reports of exenatide increasing the mass of β-cells, in addition to its glucose-lowering effects, provide encouragement for its use in the treatment of LADA.

There are a few studies evaluating GLP-1 (and exendin-4) in subjects with type 1 diabetes, and they showed reduction of fasting hyperglycemia and glycemic excursions after a meal, accompanied by inhibition of abnormal rises of blood levels of glucagon (40). Additionally, in islet transplant recipients, exendin-4 has stimulated insulin secretion and demonstrated an ability to reduce exogenous insulin requirements. Current clinical trials test the hypothesis that its use at the time of islet transplantation might be of help in preserving islet mass (41). Although not evaluated yet in LADA, these agents have a potential therapeutic value in such a setting.

Immune modulation

Since LADA is an autoimmune disease caused by failure to maintain tolerance to autoantigens, targeting them through administration of autoantigen in a tolerogenic regimen should provide an effective means of controlling the autoimmune process by inducing tolerance through deviation of the Th1 phenotype of the antigen-reactive cells toward a Th2 phenotype.

The beneficial effect of an immune intervention in LADA in protecting residual β-cell function may be hampered by several factors such as age at diagnosis, metabolic control, and extension of β-cell destruction. The latter is influenced by HLA genotypes (42). Whether different HLA genotypes associated with LADA may affect the outcome in terms of β-cell function is still unknown, but recent data seem to indicate that patients possessing a moderate- or low-risk HLA genotype, as is the case in LADA, have a higher residual β-cell function (42). We may speculate that LADA patients with such genotypes might benefit more in terms of β-cell protection after immune intervention.

The antigens that have been used so far as tolerogens in LADA have included the following: insulin, GAD, heat shock protein (HSP), and their constituent peptides.

Peptide of HSP60 (DiaPep277). HSP60 is a ubiquitous protein, part of a highly conserved family of intracellular chaperones, also located in the mitochondria and mature insulin–secretory granules of pancreatic β-cells, with an important regulatory role in the innate immune system (43) and considered an important autoantigen in diabetes. The dominant epitope of HSP60 was found to be peptide HSP277, and its modified form, DiaPep277 (generated to increase its stability in vivo), has been used in patients with recent-onset type 1 diabetes for prevention of further β-cell loss (44,45). DiaPep277 has shown suggestive evidence of better preservation of C-peptide, since at the end of the follow-up period, the intervention group had improved mean C-peptide levels and required significantly less exogenous insulin to obtain similar A1C as the placebo group. Interestingly, the drug treated group had a

shift of the T-cell response to HSP60 from a proinflammatory Th1 to a predominant Th2 phenotype (with interleukin [IL]-10 and IL-13) (44).

A phase II double-blind multicenter RCT has been conducted in 60 patients with LADA, 30–50 years old, and within 2 to 60 months after diagnosis for evaluation of safety, tolerability, and clinical, metabolic, and immunological efficacy of multiple subcutaneous doses of DiaPep277 (46). Results have not yet been published, but a brief report suggests good safety and tolerability and possible response to DiaPep277 in these patients (46).

GAD65 (Diamyd). The 65-kDa isoform of GAD (GAD65) is found in β-cells (and other tissues) and considered a major autoantigen in autoimmune diabetes (47). A large body of evidence has indicated that antibodies to GAD65 may be found in 70–75% of type 1 diabetic patients and that GADA is the most sensitive autoantibody marker for LADA (8).

An alum-formulated recombinant human form of GAD65 (Diamyd) has been evaluated in 47 patients with LADA in a dose-escalation double-blind phase II RCT (48). After 24 weeks, the 20 μg dose group showed an increase from baseline in the mean log FCP and stimulated log C-peptide. These changes were accompanied by an increase of the purported Tregs subsets ($CD4^+CD25^+/CD4^+CD25^-$ cell ratio) in the peripheral blood. With regards to glycemic control, an increase in the FBG and A1C was seen in no-effect dose groups (placebo and 4 μg), but in comparison, a decrease of these parameters was noted in the groups receiving higher doses (20, 100, and 500 μg). No study-related adverse effects were reported. A more recent study in pediatric type 1 diabetic subjects indicated that GAD-alum treatment had no significant effect on FCP after 15 months, but after 30 months, FCP and stimulated C-peptide showed a significantly smaller decline compared with placebo (although this apparent protective effect was seen only in subjects treated <6 months after diagnosis and was not accompanied by change in insulin requirement) (49). Further studies are required in the setting of LADA.

Anti-CD3 monoclonal antibodies (anti-CD3). Because the initial antigenic repertoire as the primary target of the immune attack in autoimmune diabetes is still not well defined, considerable efforts have been devoted to nonantigenic immune interventions. Although the exact mechanisms responsible for the actions of the anti-CD3 are still not fully elucidated, there are several possibilities: induction of antigenic modulation, anergy, and/or apoptosis in activated cells and immune tolerance through adaptive Tregs (50). Noteworthy outcomes have been seen in two studies in new-onset type 1 diabetes using two different humanized anti-CD3, and both have reported preservation of β-cell function with maintenance of higher endogenous insulin secretion assessed by CPR and concomitant reduction in A1C levels and insulin usage in the treated group over at least 1 year (51,52). This could be a possible beneficial intervention also for LADA patients, but studies are required to confirm the feasibility of anti-CD3 therapy for this group.

CONCLUSIONS

— A number of attractive therapeutic interventions may be envisioned for prevention of β-cell deterioration and progression toward insulin dependency, which include hypoglycemic and immunomodulatory agents, and possibly a combination of those, provided they are safe. Because the autoimmune process in LADA is thought to be slower than in childhood type 1 diabetes, there is a larger window of opportunities for intervention. An appropriate therapeutic approach would be one that offers a good metabolic control and at the same time improves the natural history of the disease (i.e., maintains/increases the residual β-cell mass and/or function).

There are no current guidelines for treatment of LADA, since this condition still has no clear definition. While waiting for the results of current and future studies, a couple of points should be taken into consideration emerging from the few studies that have evaluated interventions for LADA (reviewed here), even though their results are difficult to generalize. Sulfonylureas seemed to provide either similar or poorer glycemic control than insulin alone and caused earlier insulin dependence. Therefore, until proven contrary, sulfonylureas should not be used as first-line therapy. Small doses of insulin given early after diagnosis might be beneficial in maintaining stimulated C-peptide values and thus, supposedly, β-cell function. Hypoglycemic agents like TZD or exenatide, which also have potential beneficial effects on preservation/augmentation of β-cell mass, might be a good therapeutic option, but this has to be confirmed by clinical trials. Considering the autoimmune pathogenesis, therapies using immunomodulatory agents might be of benefit, but clinical studies should clearly demonstrate their benefit in LADA before future treatment plans could incorporate them in the effort to arrest the progression of disease.

Obviously, high-quality studies are further needed to evaluate various aspects of this form of autoimmune disease and to define the best strategy for treating it.

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