Early Insulin Treatment in Type 2 Diabetes

What are the pros?

LUIGI F. MENEGHINI, MD, MBA

The prevalence of diabetes in the world is growing at an unprecedented rate and rapidly becoming a health concern and burden in both developed and developing countries (1). In addition, we are now witnessing an upsurge in the incidence of type 2 diabetes in children and adolescents, with the potential of translating into a future catastrophic disease burden as vascular complications of the disease begin affecting a younger population. Although there may be contention regarding the impact of lowering glycemia on macrovascular disease risk, there is strong consensus of the definite benefits of lowering blood glucose to reduce the risk of retinopathy and nephropathy in either type 1 or type 2 diabetes (2,3). Despite supporting data and multiple guidelines advanced by professional organizations, overall glycemic control falls far below expectations (4). Overall, <36% of individuals with diabetes are at recommended glycemic targets, with the most difficult-to-control cases represented by insulin-deficient individuals on insulin therapy to manage their diabetes (4). Furthermore, as β-cell dysfunction progresses over time, many patients with type 2 diabetes, treated with oral agents, fail to achieve or maintain adequate glycemic control. Unfortunately, in many of these cases, antiglycemic therapy is not adjusted or advanced, thereby exposing patients to prolonged hyperglycemia and the increased risk of diabetes-related complications. The term "clinical inertia," which has come to define the lack of initiation, or intensification of therapy when clinically indicated (5), is most pronounced in the setting of insulin initiation. Subjects with type 2 diabetes, managed in a large integrated health care system, were initiated on additional blood glucose–lowering treatment only when the mean baseline A1C reached a value of 9.0% (6). Patients started on insulin had an even higher mean A1C of 9.6% and tended to have more severe baseline complications and comorbidities than those started on sulfonylurea, or metformin therapy. In addition, the higher the starting A1C when therapy was initiated or changed, the less likely the patient was of achieving adequate glycemic control (6). Although specialists are slightly more proficient than general practitioners in intensifying diabetes therapy when warranted (7), overall clinical inertia results in the majority of patients failing to achieve, or maintain, adequate metabolic goals from a period of months to several years (8,9). In summary, to improve these suboptimal metabolic outcomes, and reduce the risk of disease-related complications, more intensive management of glycemia is warranted, including the option of introducing insulin therapy earlier than the current widely practiced substandard of care.

INTRODUCTION OF INSULIN EARLIER IN THE TREATMENT PARADIGM

— Typically, whereas introducing insulin therapy in a more timely fashion would significantly improve glycemic control among subjects with type 2 diabetes, the question of insulin initiation timing in relation to other antiglycemic therapies is the subject of considerable debate (10). While insulin administration has the potential of achieving the most effective reductions in glycemic control, the initiation of insulin therapy requires greater use of resources, time, and effort from provider and patient alike, compared with oral antidiabetic therapies (11). Patient resistance to the use of insulin therapy remains a challenge, especially in populations that may have misgivings and misconceptions regarding the role of insulin replacement in diabetes management.

Notwithstanding these issues, there are specific populations that would clearly benefit from early, aggressive, and targeted introduction of insulin therapy. For instance, patients presenting with significant hyperglycemia may benefit from timely initiation of insulin therapy that can effectively and rapidly correct their metabolic imbalance and reverse the deleterious effects of excessive glucose (glucotoxicity) and lipid (lipotoxicity) exposure on β-cell function and insulin action (12). In vitro studies have demonstrated that chronic hyperglycemia leads to increased production of reactive oxygen species, and subsequent oxidative stress, which appears to affect insulin promoter activity (PDX-1 and MafA binding) and results in diminished insulin gene expression in glucotoxic β-cells (13). Interestingly, in vitro experiments have shown that these glucotoxic effects occur in a continuum of glucose concentrations (no clear threshold effect), are reversible with reinstitution of euglycemic conditions, and result in the greatest recovery of β-cell function with shorter periods of exposure to hyperglycemia (14). Various studies have demonstrated improvement in insulin sensitivity and β-cell function after correction of hyperglycemia with intensive insulin therapy (15).

INTENSIVE INSULIN TREATMENT AND β-CELL FUNCTION

— A number of trials have evaluated the strategy of implementing short-term aggressive insulin replacement as first-line therapy in the management of hyperglycemia in newly diagnosed type 2 diabetes (Table 1), with the goal of improving and preserving β-cell function, reducing insulin resistance, and maintaining optimal glycemic control through disease "remission" (16–18). In these studies, intensive insulin therapy was delivered via multiple daily insulin injections, or insulin pump ther-

From the Division of Endocrinology, Diabetes and Metabolism and the Diabetes Research Institute, University of Miami Miller School of Medicine, Miami, Florida.
Corresponding author: Luigi F. Meneghini, lmeneghi@med.miami.edu.
The publication of this supplement was made possible in part by unrestricted educational grants from Eli Lilly, Ethicon Endo-Surgery, Generex Biotechnology, Hoffmann-La Roche, Johnson & Johnson, LifeScan, Medtronic, MSD, Novo Nordisk, Pfizer, sanofi-aventis, and WorldWIDE.
DOI: 10.2337/dc09-S320
© 2009 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See http://creativecommons.org/licenses/by-nc-nd/3.0/ for details.

Table 1—*Baseline characteristics and outcomes of patients with type 2 diabetes receiving temporary insulin therapy at disease diagnosis*

	n	Age	BMI	Baseline A1C (%)	Insulin dose (units · kg^{-1} · day^{-1})	Days to glycemic control	Duration insulin therapy (weeks)	% Early responders	% Sustained responders	Weight change
Ilkova et al. (17)	13	50	27	11.2	0.61	1.9	2	92	69 (26 months)	0.4 kg
Li et al. (16)	126	50	25	10.0	0.7	6.3	2	90	42 (24 months)	−0.04 kg/m^2
Ryan et al. (18)	16	52	31	11.8	0.37–0.73	<14	2–3	88	44 (12 months)	−0.5 kg/m^2

Early responders are subjects who achieved euglycemia with insulin treatment, and late responders are subjects who maintained long-term euglycemia without pharmacotherapy after the initial insulin treatment.

apy (continuous subcutaneous insulin infusion), over a period of 2–3 weeks, with achievement of euglycemia in ~90% of subjects on completion of insulin treatment. After insulin withdrawal, patients were maintained on diet therapy only, with 42–69% maintaining euglycemia 12 or more months after treatment. Patients who achieved and maintained long-term euglycemia tended to have a better response to insulin therapy, as well as associated improvements in β-cell function, including first-phase insulin release, as measured by homeostasis model assessment of β-cell function (HOMA-B) and intravenous glucose tolerance tests.

Improvements in β-cell function and insulin action have also been reported when euglycemia is achieved with noninsulin therapies (19). Unfortunately, as illustrated by the U.K. Prospective Diabetes Study, long-term glycemic control in type 2 diabetes is difficult to maintain, regardless of the therapeutic intervention due, in part, to progressive loss of β-cell function over time. The recently published A Diabetes Outcome Progression Trial (ADOPT) demonstrated longer maintenance of glycemic control in patients using a thiazolidinedione (rosiglitazone) compared with glyburide or metformin monotherapy, although β-cell function, as measured by HOMA-B was no different at the end of the trial between the rosiglitazone and sulfonylurea groups (20); the benefits in durability of control seemed to have been a result of improved insulin sensitivity.

A recent study comparing intensive insulin therapy (multiple daily insulin injections or continuous subcutaneous insulin infusion) with oral hypoglycemic agents (glicazide and/or metformin) in newly diagnosed patients with type 2 diabetes provided some provocative results (21). In this trial, 92% of 382 subjects with poorly controlled diabetes achieved glycemic targets (fasting and 2-h postprandial capillary glucose levels of <110 mg/dl and <144 mg/dl, respectively) within an average of 8 days from start of therapy (Table 2). Treatment was withdrawn after 2 weeks of normoglycemia, followed by diet and exercise management. A greater proportion of patients randomized to intensive insulin therapy achieved glycemic targets and did so in a shorter period compared with oral agent therapy (Table 2). Shortly after discontinuing antiglycemic treatment, measures of first-phase insulin release, HOMA-B and HOMA-IR were similar among all treatment groups. By the end of 1 year, remission rates were significantly higher in the groups that had received initial insulin therapy (51 and 45% in the continuous subcutaneous insulin infusion and multiple daily insulin injections groups, respectively), compared with 27% in the oral therapy group. Whereas in the oral agent group, acute insulin response at 1 year declined significantly compared with immediate post-treatment, it was maintained in the insulin treatment groups. Of note, responders typically had higher BMI, less baseline hyperglycemia, and greater responsiveness to therapy than nonresponders.

Table 2—*Baseline characteristics and clinical outcomes comparing subjects treated with insulin or oral agent therapies lasting for 2 weeks after achievement of normoglycemia*

	Continuous subcutaneous insulin infusion	Multiple daily injections	Oral agents
n	133	118	101
Age (yrs)	50	51	52
BMI (kg/m^2)	25	24	25
Baseline A1C (%)	9.8	9.7	9.5
% Achieving euglycemia	97	95	83
Time to euglycemia (days)	4	5.6	9.3
Daily drug doses	0.68 units/kg (mean)	0.74 units/kg (mean)	Glicazide 160 mg + metformin 1,500 mg (max median)
Δ in AIR* (pmol · l^{-1} · min^{-1})	951	800	831
AIR (median) in remission groups at 1 year	809	729	335†

From Weng et al. (21). *Change in median AIR (acute insulin response) between baseline and treatment end. †$P < 0.05$ compared with continuous subcutaneous insulin infusion.

Another study comparing early and continued insulin treatment versus oral agent therapy (glibenclamide) over a period of 2 years in recently diagnosed patients with type 2 diabetes showed better long-term glycemic control and β-cell function in the insulin-treated group (22). There was no difference in weight gain between insulin and oral agent therapy and no reported cases of severe hypoglycemia, reflecting easier-to-manage glycemia, probably as a result of better endogenous insulin production.

POTENTIAL PHYSIOLOGICAL EFFECTS OF INSULIN REPLACEMENT THERAPY

— What could account for some of the differences in β-cell function seen in studies with early aggressive insu-

lin therapy? A study evaluating the anti-inflammatory effects of an insulin infusion on obese subjects without diabetes demonstrated suppression of nuclear factor κB. Nuclear factor κB is the key transcription factor responsible for the transcription of proinflammatory cytokines, adhesion molecules and enzymes responsible for producing reactive oxygen species (23). As a consequence, insulin infusion significantly suppressed generation of reactive oxygen species and decreased concentrations of plasma soluble intercellular adhesion molecule-1 (sICAM-1), monocyte chemo-attractant protein-1 (MCP-1), and plasminogen activator inhibitor-1 (PAI-1), among other observed anti-inflammatory actions (24).

Could the timing of the intervention affect the metabolic response to insulin therapy? For example, loss of first-phase insulin response, possibly as a consequence of glucotoxicity, is evident with fasting plasma glucose concentrations >115 mg/dl (25). Often, when diabetes is diagnosed, fasting plasma glucose levels are usually significantly higher, and may have been so for quite some time (26), exposing β-cells to chronic hyperglycemia and consequent β-cell decompensation (13). It could be hypothesized that early aggressive physiologic insulin replacement with both prandial and basal coverage results in rapid improvement in glucolipotoxicity, reduction of the inflammatory milieu, and consequent greater preservation of β-cell function. Some of these improvements in β-cell function were also evident after rigorous management with glyburide and metformin.

INSULIN REPLACEMENT OPTIONS AND STRATEGIES —

Whereas the use of insulin therapy in newly diagnosed subjects with type 2 diabetes appears to be associated with a low risk of hypoglycemia and weight gain, the use of algorithm-driven insulin replacement in more advanced disease is often associated with a greater incidence of weight gain and hypoglycemia. Individualizing the insulin prescription may minimize some of these adverse outcomes. Using the A1C status of a patient, the fasting blood glucose, and if available, the postprandial glucose could assist the provider in individualizing insulin replacement. Published trials in suboptimally controlled insulin-naive type 2 diabetes seem to indicate that basal insulin replacement yields similar effectiveness, but with less weight gain, and hypoglycemia risk than basal/prandial or mixed insulin strategies, when baseline A1C is ≤8.5% (27). Thus, in a patient whose predominant glycemic burden occurs overnight and whose A1C level is within 1–2% points of target, starting with a low dose of basal insulin (0.2 units · kg^{-1} · day^{-1}) and adjusting the dose to achieve fasting blood glucose levels <110–130 mg/dl often proves an effective strategy. With higher A1C levels, replacing prandial insulin, with or without basal insulin coverage, results in greater A1C reduction than basal-only replacement, albeit at the expense of more weight gain and hypoglycemia (28). For example, patients inadequately controlled on basal insulin can be started on one or more doses of rapid-acting insulin (0.05 units/kg/meal) before one or more meals (usually the largest meals), and the insulin dose titrated to achieve postprandial blood glucose levels <180 mg/dl. A basal/bolus insulin replacement, giving patients flexible prandial dosing instructions, as opposed to fixed doses of premeal insulin, has been shown to be associated with equivalent glycemic control, but with less weight gain (29). Furthermore, the use of basal insulin analogs (glargine or detemir) is associated with less hypoglycemia (especially nocturnal hypoglycemia) and, in the case of insulin detemir, less weight gain than human NPH insulin (27,30).

CONCLUSIONS —

In summary, aggressive and often temporary use of insulin therapy at disease onset in type 2 diabetes is associated with effective glycemic control with minimal weight gain and hypoglycemia. Early restitution of physiologic insulin secretion and glycemic control could be, in theory, followed by therapies to prolong maintenance of euglycemia, such as thiazolidinediones- (20) or glucagons-like peptide 1–based interventions (to date not clinically tested). A more timely and selective introduction of insulin replacement therapy, as β-cell function progresses, could facilitate the achievement and maintenance of euglycemia and thus reduce disease-associated complications.

Acknowledgments— L.F.M. has received grant support from sanofi-aventis, Novo Nordisk, Hoffmann-La Roche, and Medtronic; consulting fees from Novo Nordisk and NIPRO; and speaker's fees from sanofi-aventis, Eli Lilly, Merck, and Amylin.

No other potential conflicts of interest relevant to this article were reported.

References

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047–1053
2. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
3. UKPDS Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853
4. Koro CE, Bowlin SJ, Bourgeois N, Fedder DO. Glycemic control from 1988 to 2000 among U.S. adults diagnosed with type 2 diabetes: a preliminary report. Diabetes Care 2004;27:17–20
5. Phillips LS, Branch WT, Cook CB, Doyle JP, El-Kebbi IM, Gallina DL, Miller CD, Ziemer DC, Barnes CS. Clinical inertia. Ann Intern Med 2001;135:825–834
6. Karter AJ, Moffet HH, Liu J, Parker MM, Ahmed AT, Go AS, Selby JV. Glycemic response to newly initiated diabetes therapies. Am J Manag Care 2007;13:598–606
7. Shah BR, Hux JE, Laupacis A, Zinman B, van Walraven C. Clinical inertia in response to inadequate glycemic control: do specialists differ from primary care physicians? Diabetes Care 2005;28:600-606
8. Rubino A, McQuay LJ, Gough SC, Kvasz M, Tennis P. Delayed initiation of subcutaneous insulin therapy after failure of oral glucose-lowering agents in patients with type 2 diabetes: a population-based analysis in the UK. Diabet Med 2007;24:1412–1418
9. Grant RW, Cagliero E, Dubey AK, Gildes-Game C, Chueh HC, Barry MJ, Singer DE, Nathan DM, Meigs JB. Clinical inertia in the management of type 2 diabetes metabolic risk factors. Diabet Med 2004;21:150–155
10. Goldberg RB, Holman R, Drucker DJ. Management of type 2 diabetes. N Engl J Med 2008;358:293–297
11. Davidson MB. Early insulin therapy for type 2 diabetic patients: more cost than benefit. Diabetes Care 2005;28:222–224
12. Unger RH, Grundy S. Hyperglycemia as an inducer as well as a consequence of impaired islet cell function and insulin resistance: implications for the management of diabetes. Diabetologia 1985;28:119–121
13. Poitout V, Robertson RP. Glucolipotoxic-

ity: fuel excess and beta-cell dysfunction. Endocr Rev 2008;29;351–366
14. Gleason CE, Gonzalez M, Harmon JS, Robertson RP. Determinants of glucose toxicity and its reversibility in the pancreatic islet beta-cell line, HIT-T15. Am J Physiol Endocrinol Metab 2000;279: E997–E1002
15. Garvey WT, Olefsky JM, Griffin J, Hamman RF, Kolterman OG. The effect of insulin treatment on insulin secretion and insulin action in type II diabetes mellitus. Diabetes 1985;34:222–234
16. Li Y, Xu W, Liao Z, Yao B, Chen X, Huang Z, Hu G, Weng J. Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients is associated with improvement of beta-cell function. Diabetes Care 2004;27:2597–2602
17. Ilkova H, Glaser B, Tunçkale A, Bagriaçik N, Cerasi E. Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients by transient intensive insulin treatment. Diabetes Care 1997;20: 1353–1356
18. Ryan EA, Imes S, Wallace C. Short-term intensive insulin therapy in newly diagnosed type 2 diabetes. Diabetes Care 2004;27:1028–1032
19. Peters AL, Davidson MB. Maximal dose glyburide therapy in markedly symptomatic patients with type 2 diabetes: a new use for an old friend. J Clin Endocrinol Metab 1996;81:2423–2427
20. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, Kravitz BG, Lachin JM, O'Neill MC, Zinman B, Viberti G, ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006; 355:2427–2443
21. Weng J, Li Y, Xu W, Shi L, Zhang Q, Zhu D, Hu Y, Zhou Z, Yan X, Tian H, Ran X, Luo Z, Xian J, Yan L, Li F, Zeng L, Chen Y, Yang L, Yan S, Liu J, Li M, Fu Z, Cheng H. Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. Lancet 2008;371:1753-1760
22. Alvarsson M, Sundkvist G, Lager I, Henricson M, Berntorp K, Fernqvist-Forbes E, Steen L, Westermark G, Westermark P, Orn T, Grill V. Beneficial effects of insulin versus sulphonylurea on insulin secretion and metabolic control in recently diagnosed type 2 diabetic patients. Diabetes Care 2003;26:2231–2237
23. Dandona P, Aljada A, Mohanty P, Ghanim H, Hamouda W, Assian E, Ahmad S. Insulin inhibits intranuclear factor kB and stimulates IkB in mononuclear cells in obese subjects: evidence for an anti-inflammatory effect? J Clin Endocrinol Metab 2001;86:3257–3265
24. Dandona P, Chaudhuri A, Mohanty P, Ghanim H. Anti-inflammatory effects on insulin. Curr Opin Clin Nutr Metabol Care 2007;10:511–517
25. Brunzell JD, Robertson RP, Lerner RL, Hazzard WR, Ensinck JW, Bierman EL, Porte D Jr: Relationships between fasting plasma glucose levels and insulin secretion during intravenous glucose tolerance tests. J Clin Endocrinol Metab 1976;42: 222–229
26. Samuels TA, Cohen D, Brancati FL, Coresh J, Kao WH. Delayed diagnosis of incident type 2 diabetes mellitus in the ARIC study. Am J Manag Care 2006;12: 717–724
27. Riddle MC, Rosenstock J, Gerich J. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003;26:3080–3086
28. Holman RR, Thorne KI, Farmer AJ, Davies MJ, Keenan JF, Paul S, Levy JC. 4-T Study Group: Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. N Engl J Med 2007;357: 1716–1730
29. Bergenstal RM, Johnson ML, Powers MA, Wynne A, Vlajnic A, Hollander PA. Using a simple algorithm (ALG) to adjust mealtime glulisine (GLU) based on pre-prandial glucose patterns is a safe and effective alternative to carbohydrate counting (Carb Count) (Abstract). Diabetes 2006; 55 (Suppl. 1):A105
30. Philis-Tsimikas A, Charpentier G, Clauson P, Ravn GM, Roberts VL, Thorsteinsson B. Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. Clin Ther 2006;28:1569–1581