When Intensive Insulin Therapy (MDI) Fails in Patients With Type 2 Diabetes: Switching to GLP-1 Receptor Agonist Versus Insulin Pump

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Treatment with insulin, alone or with oral or injectable hypoglycemic agents, is becoming increasingly common in patients with type 2 diabetes. However, approximately 40% of patients fail to reach their glycemic targets with the initially prescribed regimen and require intensification of insulin therapy, which increases the risks of weight gain and hypoglycemia. Many of these patients eventually reach a state in which further increases in the insulin dosage fail to improve glycemic control while increasing the risks of weight gain and hypoglycemia. The recently completed OpT2mise clinical trial showed that continuous subcutaneous insulin infusion (CSII) is more effective in reducing glycated hemoglobin (HbA_{1c}) than intensification of multiple daily injection (MDI) insulin therapy in patients with type 2 diabetes who do not respond to intensive insulin therapy. CSII therapy may also be useful in patients who do not reach glycemic targets despite multidrug therapy with basal-bolus insulin and other agents, including glucagon-like peptide (GLP)-1 receptor agonists; current guidelines offer no recommendations for the treatment of such patients. Importantly, insulin and GLP-1 receptor agonists have complementary effects on glycemia and, hence, can be used either sequentially or in combination in the initial management of diabetes. Patients who have not previously failed GLP-1 receptor agonist therapy may show reduction in weight and insulin dose, in addition to moderate improvement in HbA_{1c}, when GLP-1 receptor agonist therapy is added to MDI regimens. In subjects with long-standing type 2 diabetes who do not respond to intensive insulin therapies, switching from MDI to CSII and/or the addition of GLP-1 receptor agonists to MDI have the potential to improve glycemic control without increasing the risk of adverse events.

Type 2 diabetes is a progressive disease caused by increasingly severe β-cell dysfunction (1). Preventive strategies have been unsuccessful in curbing the increase in the prevalence of the disease (2), and although more than 10 classes of hypoglycemic medications have been developed to treat type 2 diabetes, none have been shown to ensure robust, sustained glycemic control over the course of the disease (3). As a result, increasing numbers of patients are being treated with insulin alone or, more commonly, as an adjunct to oral or injectable hypoglycemic therapy. However, ~40% of patients treated with this approach fail to achieve their glycated hemoglobin (HbA_{1c}) targets with basal insulin therapy and require additional treatment with boluses of short-acting insulin preparations (4). Unfortunately, in some

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patients, these intensified insulin regimens also eventually prove to be ineffective in ensuring glycemic control, and they often increase the risk of adverse events such as weight gain and hypoglycemia (5). The mechanisms underlying this loss of response have not been extensively studied.

When a multiple daily injection (MDI) regimen fails to achieve the target HbA_{1c}, there are some options available to patients, including adding glucagon-like peptide 1 (GLP-1) receptor agonists (GLP-1 RAs), adding sodium–glucose cotransporter 2 inhibitors, or undergoing bariatric surgery. The recently completed randomized, open-label trial OpT2mise (6) has provided evidence that continuous subcutaneous insulin infusion (CSII) is more effective in reducing HbA_{1c} levels than intensification of MDI insulin therapy in patients with type 2 diabetes in whom adequate glycemic control cannot be achieved with intensive basal-bolus insulin regimens. This article will focus on two of these options: adding GLP-1 RA to MDI and switching from MDI to CSII.

We performed a literature review to identify published studies in English of patients with type 2 diabetes treated with MDI and failing to reach glycemic goals using the following MeSH (Medical Subject Headings) terms search string: ("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields] OR "diabetes mellitus type 2"[All Fields]) AND (mdi[All Fields] OR (multiple[All Fields] AND daily[All Fields] AND ("injections"[MeSH Terms] OR "injections"[All Fields]))) AND ("2006/02/09"[PDat]: "2015/02/06"[PDat]). A total of 112 hits were identified by the PubMed search; 91 references were excluded. Of the remaining 18 articles, 4 were on the addition of pioglitazone, acarbose empagliflozin, and sitagliptin (1 article per drug); 2 on the addition of GLP-1 RAs; and 15 on CSII in type 2 diabetes.

WHAT EVIDENCE DO WE HAVE THAT CSII MIGHT OFFER BENEFITS FOR PATIENTS WITH TYPE 2 DIABETES THAT IS POORLY CONTROLLED WITH MDI INSULIN THERAPY?

Four randomized controlled studies have compared the efficacies of pump treatment and MDI in lowering HbA_{1c} in patients with type 2 diabetes (5). In the two trials with parallel-group designs, the benefits of pump therapy were similar to those of intensified MDI treatment (7,8), whereas the two randomized crossover studies (9,10) found that pump treatment was superior to MDI.

A larger randomized controlled trial, OpT2mise (6), was designed to resolve this discrepancy. In this study, >300 patients in whom adequate glycemic control was not achieved despite optimized MDI therapy were randomized to ongoing treatment with either optimized MDI insulin therapy or CSII. After 6 months of treatment, the mean (SD) HbA_{1c} level had decreased by 1.1 (1.2)% (12 [13] mmol/mol) in the CSII group compared with only 0.4 (1.1)% (4 [12] mmol/mol) in the MDI group—a highly significant difference of –0.7% (95% CI –0.9 to –0.4) (–8 mmol/mol [95% CI –10 to –4]), $P < 0.0001$). The improved glycemic control achieved with pump therapy was independent of age, sex, cognitive state, fasting C-peptide levels, and anti-GAD antibody status. In addition, insulin doses in the pump therapy group were 20% lower than those of the group managed with MDI, and no significant between-group differences were observed in the rates of severe adverse events or hypoglycemia, which were low in both cases.

WHAT KIND OF PATIENTS WITH TYPE 2 DIABETES MIGHT BE EXPECTED TO BENEFIT FROM A SWITCH FROM MDI TO PUMP THERAPY?

Type 2 diabetes is a heterogeneous disease at both the phenotype and genotype levels. Interactions between genetic, environmental, and behavioral factors—not to mention those related to the microbiota (11)—result in substantial phenotypic variability, and, as noted above, this variability is reflected in the heterogeneous responses to different drugs. This is the reason so much emphasis is currently being placed on the importance of "precision medicine," whereby therapy is tailored to the specific needs and characteristics of the individual patient.

One of the major strengths of the OpT2mise trial, compared with previous comparisons of MDI with pump therapy, is that it focused selectively on a very well-defined subpopulation of patients with type 2 diabetes whose needs are a major challenge for diabetologists the world over: patients who were insulin resistant and had HbA_{1c} levels that remained >8% (64 mmol/mol) after ≥3 months of aggressive multidrug treatment. This treatment included at least three daily injections of insulin analogs (rapid- and long acting) and an additional 2-month period of dose titration to a minimum total dose of 0.7 units/kg/day (12). The characteristics of these patients, which are shown in Table 1, are similar to those of patients with type 2 diabetes who have benefited from CSII in French cohort studies (13,14): late-middle-aged individuals with long-standing diabetes, level I obesity, and a mean HbA_{1c} level that remains above the target range, despite aggressive treatment.

Patients of this type are by no means rare in routine clinical practice. In fact, the Swedish National Diabetes Register (the world's most comprehensive national diabetes registry) recently reported that HbA_{1c} levels >8.8% (73 mmol/mol) are present in almost 1 in 10 patients with type 2 diabetes and >1 in 5 of those being treated in specialist clinics. Furthermore, most of these individuals are already being treated with insulin, alone or with other hypoglycemic medications (15). Of note, CSII as replacement of MDI for intensive insulin therapy has safety concerns with respect to cardiovascular and all-cause mortality similar to those of MDI, as discussed in recent publications (16,17).

WHAT ARE THE PATIENT EDUCATION NEEDS NECESSARY FOR CSII TREATMENT IN TYPE 2 DIABETES?

Device handling for patients with type 2 diabetes with age- and diabetes-related cognitive and dexterity decline might be complicated with current pump devices (5). In the OpT2mise study, patients assigned to pump treatment underwent up to 3 weeks' training with additional visits (6). Simplifying future pumps and related procedures with use of prefilled cartridges can potentially be advantageous. Experience from several cohorts and data from the OpT2mise study demonstrate that need for complex bolus dosing, meal carbohydrate estimates, and multiple basal rates are not necessary in most patients with type 2 diabetes (as opposed to the case in patients with type 1 diabetes) and that the majority of patients attain autonomy in the use of CSII (18).

Table 1—Baseline characteristics of patients with type 2 diabetes enrolled in the OpT2mise study (6)

	CSII pump therapy (n = 168)	MDI therapy (n = 163)
Age (years)	55.5 (9.7)	56.4 (9.5)
Sex (male/female), *n* (%)	94 (56.0)/74 (44.0)	86 (52.8)/77 (47.2)
Ethnic origin, *n* (%)		
Caucasian	162 (96.4)	156 (95.7)
Black African	6 (3.6)	7 (4.3)
Duration of diabetes (years)	14.9 (8.0)	15.3 (8.0)
HbA_{1c}, % [mmol/mol]	9.0 (0.75) [75 (8.2)]	9.0 (0.76) [75 (8.3)]
Weight (kg)	97.3 (22.6)	94.9 (22.0)
BMI (kg/m^2)	33.5 (7.5)	33.2 (7.0)
Systolic blood pressure (mmHg)	132.3 (15.2)	131.9 (14.8)
Diastolic blood pressure (mmHg)	75.6 (9.4)	76.0 (10.6)
Total cholesterol (mmol/L)	4.5 (1.4)	4.4 (1.0)
HDL (mmol/L)	1.2 (0.4)	1.4 (0.4)
LDL (mmol/L)	2.2 (0.8)	2.2 (0.8)
Triglycerides (mmol/L)	2.3 (2.4)	1.9 (1.6)
Smokers, *n* (%)	24 (14.3)	25 (15.3)
Metformin use, *n* (%)	120 (71.4)	112 (68.7)
Metformin dose (mg/day)	1,810 (679.8)	1,788 (636.1)
Total daily insulin dose (units/kg)	1.1 (0.4)	1.1 (0.4)
Total daily insulin dose (units)	112.3 (53.9)	106.2 (49.2)
Total long-acting insulin dose (units/day)	57.4 (30.3)	52.4 (27.7)
Total rapid-acting insulin dose (units/day)	55.6 (31.7)	53.8 (30.8)
Diabetes complications and comorbidities, *n* (%)		
Dyslipidemia	26 (15.5)	16 (9.8)
Cardiac-related diseases	142 (84.5)	137 (84.0)
Peripheral vascular disease	12 (7.1)	7 (4.3)
Retinopathy	6 (3.6)	3 (1.8)
Diabetic nephropathy	22 (13.1)	12 (7.4)
Peripheral neuropathy	0 (0)	0 (0)

Data are presented as mean (SD) unless otherwise indicated.

Simple pump programming achieved significant glycemic control, not unlike more complex regimens (6), and was deemed safe and easy for use by physicians in secondary and primary clinics (19). Thus, a simple approach for pump use in type 2 diabetes management can decrease regimen complexity and encourage patients and caretakers to use CSII. While there is a need for an increase in patient interaction at the initiation of CSII therapy, the 12-month outcome of the OpT2mise study extension indicates that it has a lasting effect without further need of additional CSII-related visits (20).

WHAT PLACE DOES INSULIN PUMP THERAPY HAVE IN THE TREATMENT OF TYPE 2 DIABETES?

Transient use of intensive insulin therapy in the initial phases of type 2 diabetes is intended to preserve β-cell function, and it has been reported to significantly improve remission rates (21–23). However, most national and international guidelines recommend MDI therapy as a last resort to be implemented after all previous therapies (including oral or injectable hypoglycemic agents or combinations of these) have failed to achieve therapeutic goals (24,25). These recommendations are based on extensive clinical experience and study data, which have demonstrated the efficacy of basal-bolus insulin therapy in improving glycemic control in patients with long-standing type 2 diabetes.

As noted earlier, however, adding MDI often does not suffice. In the Treating To Target in Type 2 Diabetes (4-T) trial, ~30–50% of patients will not achieve their HbA_{1c} target with this approach, irrespective of the specific insulin regimen used (4). Similar findings have been observed in studies comparing MDI insulin therapy with premixed insulin formulations, in which ~35–40% of patients did not reach glycemic control targets with MDI regimens (26,27).

These data suggest that the needs of a significant proportion of patients are not being met with MDI regimens. Alternatives recommended by current guidelines include bariatric surgery, which is indicated only in selected cases, and the addition of other oral drugs, such as GLP-1 RAs (discussed in greater detail below): CSII is not even considered in international guidelines (24,25,28) or in national guidelines, notably, the current National Institute for Health and Care Excellence guidelines from the U.K. (29). It is to be hoped that this omission will be reconsidered in the near future, in light of the results of the OpT2mise trial. Pump therapy has also been shown to be effective in patients with type 2 diabetes during acute stages of disease and during pregnancy (30).

Cost is an important consideration for usage of a treatment by a health care system, but an in-depth discussion on cost-effectivenesss is beyond the scope of this article and has significant regional differences. Although initial costs associated with CSII are high, improvements in HbA_{1c} with a decrease in overall insulin requirements observed with CSII versus MDI may offer important reductions in diabetes-related complications and associated costs, as recently assessed in the U.K. in the setting of uncontrolled type 2 diabetes (31).

WHAT EVIDENCE DO WE HAVE THAT THE ADDITION OF GLP-1 RAs MIGHT OFFER BENEFITS FOR PATIENTS WITH TYPE 2 DIABETES THAT IS POORLY CONTROLLED WITH BASAL INSULIN THERAPY?

Insulin therapy is a very effective means of treating hyperglycemia; however, the great reluctance by patients and doctors to initiate and intensify insulin therapy means that HbA_{1c} goals are often unmet (32). GLP-1 RAs have also been shown to be effective in treating hyperglycemia and normalizing plasma glucose concentrations in patients with type 2 diabetes (33). The glucose-lowering effect of GLP-1 RA therapy is glucose dependent. Therefore, and in contrast to prandial insulin, GLP-1 RA therapy added to basal insulin is associated with a lower risk of

hypoglycemia, without compromising HbA_{1c} reduction (34,35). The lower rate of observed hypoglycemia could also be attributed to the lower insulin dose required when adding GLP-1 RA to patients on insulin regimens (36). Reduction of hypoglycemia is also related to the prevailing event rate of hypoglycemia. Patients uncontrolled on MDI who exhibit severe insulin resistance and/or a high level of obesity show low rates of hypoglycemia (6,37), thus diminishing the advantage of GLP-1 RAs in reducing hypoglycemia events while retaining their beneficial weight reduction effect (37). Here again, however, even with the highest tolerated doses of GLP-1 RAs, only approximately half of patients reach HbA_{1c} levels <7% (53 mmol/mol) (38).

A large body of evidence currently demonstrates that combining these two modalities is an advantageous approach. Basal insulin analogs provide diurnal and especially nocturnal coverage during fasting periods, reducing hepatic glucose production and resulting in improvements in nocturnal and fasting plasma glucose levels (39). GLP-1 RAs stimulate insulin secretion and suppress glucagon secretion, both in a glucose-dependent manner, with marked reductions in postprandial glucose levels (40), thereby providing a complementary mechanism of action to basal insulin. In addition, weight loss often experienced with GLP-1 RAs can counteract the weight gain caused by insulin therapy.

Randomized, placebo-controlled trials evaluating use of GLP-1 RAs in conjunction with basal insulin have demonstrated meaningful reductions in HbA_{1c}, weight loss, and low risk of hypoglycemia (41–45). Consistently, recent studies with fixed-dose mixtures of the various GLP-1 RAs classes—short-acting lixisenatide and insulin glargine (LixiLan-l phase III study)—and the completed series of studies with daily liraglutide and insulin degludec (Dual Action of Liraglutide and Insulin Degludec in Type 2 Diabetes [DUAL] studies) demonstrated the preservation of the dual effect of each component in HbA_{1c} reduction with decreasing hypoglycemia and weight gain in comparison with strategies of uptitration of basal insulin or MDI regimens. Furthermore, patients on the fixed-combination GLP-1 and basal insulin had lesser gastrointestinal side effects than seen when each component is titrated separately. A review of the studies with combined insulin degludec and liraglutide (46) demonstrated the increased odds for achieving HbA_{1c} <7.0% without hypoglycemia and no weight gain versus uptitrated insulin glargine. The improved outcome was associated with a reduction of regimen complexity related to fewer injections per day. An alternative approach for decreasing treatment complexity has been studied with once-weekly GLP-1 RA dulaglutide in the AWARD-4 trial, which studied combination therapy with insulin/GLP-1 RA in combination with insulin lispro (47). Here, the comparison was between once-weekly dulaglutide and daily glargine, both, in addition to mealtime lispro and metformin. The adjusted mean HbA_{1c} difference versus glargine was statistically significant but small (–0.25% [95% CI –0.42 to –0.07], –2.73 mmol/mol [95% CI –4.59 to –0.77]; $P = 0.005$), with no significant differences in hypoglycemia incidence and with a clinically relevant between-group weight difference of 3.2 kg. The once-weekly dose of dulaglutide was associated with improvement in several patient outcome measures (48).

Other randomized controlled trials compared the addition of GLP-1 RA versus bolus insulin in patients who had not reached HbA_{1c} goals on oral medications and basal insulin. These studies demonstrated that adding GLP-1 RA was comparable with adding prandial insulin three times a day to basal insulin therapy with regard to improving glucose control, with the added value of weight loss and less hypoglycemia and the advantage of having fewer injections, although with a higher rate of gastrointestinal side effects (49,50). From these studies, one could extrapolate that adding GLP-1 RAs to more complex MDI regimens would also be beneficial.

A substantial body of evidence is therefore in favor of combining basal insulin and GLP-1 RAs early in the course of therapy, with evidence for a lower risk of hypoglycemia and weight loss without compromising HbA_{1c} reduction compared with the addition of mealtime bolus insulin. We would also suggest that MDI refractoriness should be considered only after therapeutic trials with GLP-1 RAs have been attempted when appropriate.

ADDING GLP-1 RAs TO MDI INSULIN REGIMEN

Two randomized prospective controlled trials that investigated the effect of GLP-1 RA therapy added to intensive (basal-bolus) insulin therapy have very recently been published in the English literature (51,52). The trials' approach and objectives differed from each other and from those of the OpT2mise trial, thus precluding direct comparison between these trials (Table 2). Lane et al. (51) evaluated the effect of the addition of liraglutide to high-dose intensive insulin therapy compared with standard insulin uptitration in morbid obese insulin-resistant patients with type 2 diabetes requiring high-dose insulin therapy. The objective was to decrease weight and reduce insulin dose. Thirty-seven subjects with type 2 diabetes requiring >100 units of insulin daily administered either by CSII or by MDI with or without metformin were randomized to receive either liraglutide titrated to 1.8 mg plus insulin or intensive insulin only (control

Table 2—Comparison of prospective randomized studies on add-on therapy for patients with type 2 diabetes on MDI

	Lane et al. (51)	MDI Liraglutide trial (52)	FLAT-SUGAR (53)	OpT2mise (6)
n	37	124	102	495
Age (years)	59.7	63.7	62	56.4
Diabetes duration (years)	17.1	17.3	15	15.2
HbA_{1c} (%)	7.8	9.0	7.9	9.4
BMI (kg/m^2)	41	33.7	33.9	33.6
TDD	187	105.3		104.9
ΔHbA_{1c} (%)	−0.2	−1.1		−0.7
ΔWeight (kg)	−5.6	−3.8		0.4
ΔInsulin (units)	−46	−15.8		−25

Data are means. TDD, total daily dose.

subjects). At 6 months, subjects receiving liraglutide plus insulin experienced statistically significant reduction of 0.26% in HbA_{1c} and reductions in weight, insulin dose, and glycemic variability as measured by a continuous glucose monitor compared with the control group receiving only insulin. In the recent published MDI Liraglutide trial (52), targeting patients with HbA_{1c} uncontrolled on MDI without concomitant hypoglycemic medication (either oral or injectable) resulted in a significant reduction of 1.13% (95% CI −1.45 to −0.81; $P < 0.001$) in HbA_{1c}, with reductions in weight (mean 3.8 kg) and insulin dose (mean 15.8 units). As the patients in this study were not on concomitant medications for glycemic control for >3 months, they are not characteristic of the common practice where MDI therapy is usually added on and is combined with metformin and/or other classes of medications, including GLP-1 RAs. This study does provide evidence that GLP-1 RA therapy is effective in addition to MDI treatment in patients with long-standing diabetes and high HbA_{1c}.

Further insights into this issue may emerge from FLuctuATion reduction with inSUlin and Glp-1 Added togetheR (FLAT-SUGAR) (53), which investigated the effect of replacing preprandial short-acting insulin analogs with preprandial exenatide in patients with poorly controlled glycemia despite intensive basal-bolus insulin regimens, who were at high risk for cardiovascular events (mean age 62 years, mean duration of diabetes 15 years, mean BMI 33.9 kg/m^2, and mean baseline HbA_{1c} 7.9%). FLAT-SUGAR is not a treat-to-target study, precluding comparison of relative effectiveness efficacy of HbA_{1c} lowering with the OpT2mise trial. Preliminary findings presented at the recent American Diabetes Association 2015 Scientific Sessions indicate that basal insulin plus mealtime administration of exenatide can be as effective in reducing HbA_{1c} levels as basal-bolus insulin therapy (7.1 vs. 7.2% after 26 weeks of therapy), and it is also associated with significantly greater weight loss (4.7 kg loss vs. 0.8 kg gain in the basal-bolus insulin group; $P < 0.001$). It is interesting to note that in several respects the FLAT-SUGAR population resembles that of the OpT2mise trial, where CSII proved to be significantly more effective in reducing HbA_{1c} levels than intensive basal-bolus insulin therapy (even when the latter was combined with GLP-1 RAs or other agents) and no more likely than the latter to cause excessive weight gain. It would therefore be interesting to see how the two strategies could be combined.

A prospective, observational study by van Velsen et al. (54) investigated 125 obese patients treated with insulin in a clinical practice setting who were started on a GLP-1 RA (liraglutide or exenatide). Seventy-four patients (59%) were taking four injections of insulin per day, and three patients (2%) were on an insulin pump. The study showed that HbA_{1c} and weight decreased significantly at all time points ($P \leq 0.001$ compared with baseline; HbA_{1c} −5.5 mmol/mol [−0.5%] and weight −14.3 kg after 12 months), with the largest decrease in the first 3 months. After 6 and 12 months, the total daily insulin dose decreased significantly ($P < 0.001$; −75.4 IU after 12 months). Moreover, 34% of the patients were able to stop using insulin therapy after 12 months (excluding 19% of patients who failed to improve or stopped liraglutide medication owing to adverse effects). In short, they found that adding a GLP-1 RA to treatment of obese patients with type 2 diabetes already on insulin therapy led to a significant reduction of HbA_{1c} levels, body weight, and insulin dose.

Other retrospective studies reached similar conclusions. One study (55) evaluated the effect of exenatide 5 μg twice daily on clinical parameters in 52 obese patients with type 2 diabetes whose hyperglycemia was not adequately controlled despite treatment with oral hypoglycemic agents and insulin. Mean follow-up period was 26 weeks. The 38 patients who took exenatide regularly were compared with the 14 patients who discontinued exenatide because of insurance, personal, or economic reasons (control group). Measurements at baseline and at follow-up showed that mean body weight decreased by 6.46 ± 0.8 kg ($P < 0.001$) in the exenatide group, while it increased by 2.4 ± 0.6 kg in the control group ($P < 001$). In the exenatide group, mean HbA_{1c} decreased by 0.6 ± 0.21% ($P = 0.007$), and the insulin dosage requirement decreased for rapid-acting and mixed insulins ($P < 0.02$). In the exenatide group, there was a decrease in total cholesterol by 8.5 ± 3.3% ($P = 0.03$), triglycerides by 26 ± 7.6% ($P = 0.01$), systolic blood pressure by 9.2 ± 3.3 mmHg ($P = 0.02$), and hs-CRP by 34 ± 14.3% ($P = 0.05$). These indices did not change in the control group.

Other similar retrospective studies also concluded that the addition of a GLP-1 RA effectively treats obese patients with type 2 diabetes on insulin, leading to weight loss and reduction in levels of HbA_{1c}, total and prandial insulin doses, systolic blood pressure, triglycerides, and hs-CRP, along with a low risk of hypoglycemia (56). These improvements were also evidenced in a study where liraglutide was added to an MDI regimen in very insulin-resistant patients taking U-500 insulin with a mean daily dose of 192 units (37). After 12 weeks, liraglutide reduced HbA_{1c} by 1.4% (mean baseline HbA_{1c} 8.5%), while insulin dose was reduced by 28%. There were no reports of hypoglycemia, and body weight was reduced by 5 kg (baseline body weight 136 kg). Furthermore, the addition of GLP-1 RA to complicated MDI treatment seems to be associated with high treatment satisfaction (57), though it still remains unclear how sustainable the effect is during long-term treatment (58).

ELEMENTS THAT MAY FAVOR THE CHOICE OF ONE OR THE OTHER OPTION

As no studies directly comparing GLP-1 RA versus insulin pump are available, current knowledge and experience may suggest the following rationale in the decision-making process.

No Previous Exposure to GLP-1 RAs

Patients failing MDI, not previously treated by GLP-1 RAs, can benefit from a therapeutic trial of these drugs according to Lind et al. (52).

High HbA_{1c} Levels

At HbA_{1c} >8.5%, the advantage of CSII is more pronounced, and therefore switching patients for whom MDI failed to CSII is warranted. Addition or continuation of GLP-1 RA can then be considered (6).

High BMI

Obese patients for whom MDI failed can benefit from the weight reduction induced by GLP-1 RAs (37). Recent studies have demonstrated that increasing

liraglutide dose beyond 1.8 mg, up to 3 mg daily, can cause additional weight loss without further reductions in HbA_{1c} (59).

High Glycemic Excursions

Patients characterized by high overall glucose levels and relatively low SD and MAGE on a 24-h continuous glycemic profile, as in the OpT2mise trial (60), can successfully be treated by insulin pumps, while patients with higher postprandial glycemic excursions, as measured by SD, MAGE, or other indices, may benefit more from GLP-1 RA therapy, as suggested by Monnier and Colette (61).

CONCLUDING REMARKS

A significant proportion of patients with type 2 diabetes, moderate obesity, and long-standing disease do not reach adequate glycemic control despite intensive insulin regimens. At this stage, the only therapeutic alternative offered by current guidelines is bariatric surgery, which is still limited to selected patients.

The OpT2mise trial demonstrated that switching to insulin pump therapy can enhance insulin action in this subset of patients, without significantly increasing adverse events such as hypoglycemia and weight gain. As suggested by the recent prospective controlled trials, adding a GLP-1 RA cannot replace intensive insulin therapy, although it still may be helpful in controlling weight gain and glycemic excursions.

In conclusion, when patients on MDI regimens have still not reached their target glycemic control, while on GLP-1 RA therapy, switching to CSII is an effective option. If, alternatively, the patient is not on GLP-1 RA therapy, the addition of GLP-1 RA also shows improved glycemic control and reduced insulin doses, with the added benefit of weight loss. Large-scale registries of real-world clinical use of CSII in type 2 diabetes, providing stringent assessment of the costs, organization, education, effect on body weight, safety, and potential for durability of the glycemic control, will potentially provide additional definition of the ideal patient and further define CSII positioning with respect to new medications.

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