Future Role of Non-Insulin Antihyperglycemic Agents in the Management of Type 1 Diabetes Mellitus

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Introduction

In contrast to current approaches to Type 2 diabetes (T2DM), the management of Type 1 diabetes (T1DM) continues to be glucocentric. This is understandable considering the substantial lifetime risk of potentially devastating microvascular complications associated with the disease. Consequently, advances in the management of T1DM have largely focused on enhanced insulin preparations, technologies for insulin delivery and blood glucose monitoring. However, despite the use of these therapeutic approaches, only 21% of adults (and fewer children) reach glycemic targets associated with a lower risk of microvascular complications[1] and life expectancy in patients with T1DM is 12 years shorter than that of the general population.[2] Cardiovascular and kidney disease, together with hypoglycemia, are the major causes of mortality in patients with T1DM.[3]

Significant morbidity and mortality are associated with T1DM, but also with its treatment. The adverse effects of insulin, causing hypoglycemia (which is often a key barrier to achieving glycemic targets) and body weight gain are well known to clinicians. Insufficient attention has been paid to the burden of diabetes self-management and the negative impact of the disease and its treatment on patients' quality of life.

Should practitioners consider a broader perspective on T1DM management with the objective of reducing microvascular and macrovascular risk, while simultaneously reducing the burden of T1DM and the adverse effects of therapy? Could using non-insulin antihyperglycemic agents (NIAHAs) as adjuncts to insulin assist practitioners in achieving this objective? (**Figure 1**). The potential utility of NIAHAs in the management of T1DM is discussed in this paper.

Metformin

Based on long experience and its effect as an insulin sensitizer, metformin has been used by many physicians in the management of T1DM, particularly in individuals with obesity and/or high insulin requirements. Treatment-associated gastrointestinal (GI) side effects have been common and persistence with therapy has been variable. A small number of randomized clinical

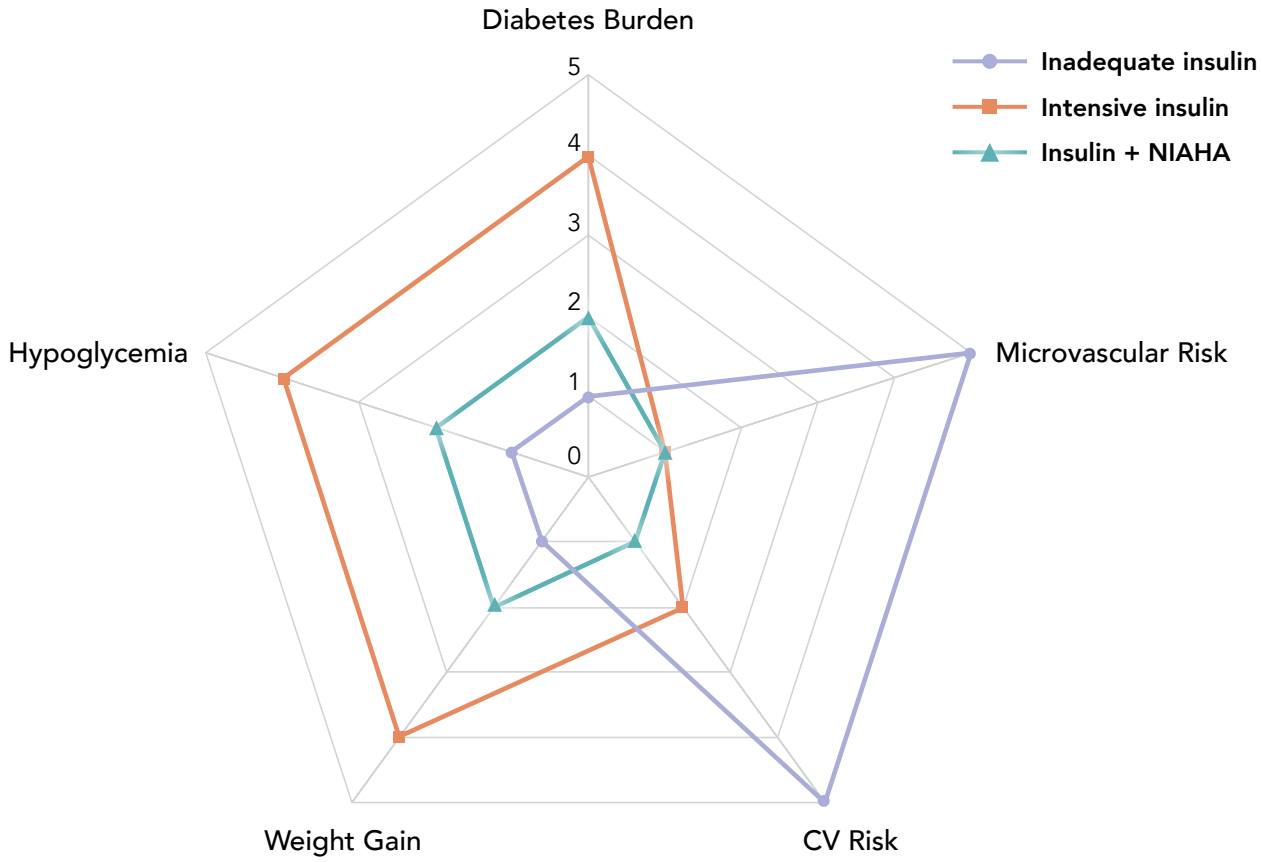

Figure 1: Hypothetical illustration of various approaches to T1DM management and their relative impact on microvascular and macrovascular systems; hypoglycemia risk; body weight gain; and diabetes burden. Inadequate insulin therapy with high A1c would be associated with high risk for microvascular and macrovascular complications, but low risk for body weight gain and hypoglycemia. Intensification of insulin therapy could reduce the risk of microvascular and macrovascular complications, but might be associated with increased disease burden, body weight gain, and risk for hypoglycemia. Adjunctive therapies (e.g., NIAHAs) which could help achieve glycemic targets without body weight gain, hypoglycemia or diabetes burden would be desirable.
Courtesy of Dr. Peter A. Senior.

trials investigating the utility of metformin in T1DM have demonstrated that metformin is associated with small, but statistically significant improvements in A1c, with lower insulin requirements, and body weight loss (Table 1).[4] The REMOVAL trial was a large, double blind, placebo-controlled clinical trial of metformin 1,000 mg bid administered to adults with T1DM >40 years of age for three years to evaluate whether or not it would slow the progression of carotid intima-media thickening (IMT).[5] Although no difference was seen in the primary outcome, maximal carotid IMT was lower with metformin. There were, however, significant reductions in body weight and low-density lipoprotein (LDL) cholesterol. Glomerular filtration rate (GFR) was stable with metformin vs a decline of 4 mL/min/1.73m^2 with placebo. There was no sustained difference in A1c or the insulin dose over three years.

GLP-1 Receptor Agonists (GLP-1RAs)

Although some of the glucose-lowering effects of incretin therapies in T2DM, mediated by enhancing glucose-dependent insulin secretion, should not apply in C-peptide negative individuals with Type 1 diabetes, other effects mediated by alteration in food intake, satiety and suppression of post-prandial glucagon levels have the potential to benefit individuals with T1DM. Furthermore, pre-clinical data suggesting an anti-apoptic effect of glucagon-like peptide (GLP) on beta cells has suggested the potential for glucagon-like peptide-1 receptor agonists (GLP-1RAs) to preserve beta cells in new-onset T1DM. However, two Phase 2 clinical trials of GLP-1RAs in new-onset T1DM showed no effect on beta cell preservation on their own but may have been helpful when combined

Agent/Class	Metformin[4,5]	GLP-1RA[9,10]	SGLT2i[13,14]
A1c	0.28% (ns)	-0.35–0.15%	0.37%
Insulin Requirements	-6.6 units	-5.5 to -1.2 units	-6.23 units
Body Weight	-1.2 kg	-3.6 kg to -4.9 kg	-2.54 kg
Blood Pressure		Short-term lowering	-2 to -4 mmHg
Hypoglycemia	=	Additional symptomatic events Severe hypoglycemia	=
CV Risk	LDL -0.13 Lower max cIMT	?	?lower LDL, triglycerides
Renal	+ 4 mL/min	No change[11]	To be tested
Other *(QoL, Variability)*		Improved TRIM-D score No difference in SF36[9,10] More TIR in pump trial[11]	Increased TIR, less variability
DKA	No increase	?Slight increase	Increases

Table 1: Impact of adjunct NIAHAs added to insulin vs placebo in clinical trials or meta-analyses on metabolic and other outcomes. *CV, cardiovascular; DKA, diabetic ketoacidosis; TRIM-D, Treatment-Related Impact Measures–Diabetes; QoL, quality of life; LDL, low-density lipoprotein; TIR, time-in-range.*
Courtesy of Dr. Peter A. Senior.

with anti-interleukin-21.[6,7] These studies were not designed to examine potential benefits for A1c or metabolic factors.

Subsequent to small, mechanistic studies of short-acting GLP-1RAs in T1DM,[8] two large clinical studies of liraglutide (0.6, 1.2, 1.8 mg/day) were conducted. One study had a treat-to-target design while the insulin dose was capped in the other study.[9,10] In both studies, liraglutide was associated with reductions in A1c, body weight and insulin dose; the effect was greater with the 1.2 mg and 1.8 mg doses (Table 1). In both studies, there were increased rates of symptomatic hypoglycemia with liraglutide, and higher rates of hyperglycemia with ketosis in subjects randomised to the 1.8 mg dose. There was no increase in nocturnal or severe hypoglycemia.[10] Sub-group analyses suggested that greater benefits may be seen in subjects with residual c-peptide.

Greater differences in A1c (-0.7%), body weight (-6.3 kg) and insulin dose (-8 units) were demonstrated in a smaller 26-week randomized, controlled clinical trial of liraglutide 1.8 mg in obese T1DM subjects using insulin pumps.[11] In this study, there was an increase in time-in-range and no increase in hypoglycemia. Treatment satisfaction as recorded in the Diabetes Treatment Satisfaction Questionnaire (DTSQc) increased to a greater extent with liraglutide than with placebo. No cases of diabetic ketoacidosis (DKA) were reported, nor any effect on GFR or albumin-to-creatinine ratio (ACR).

Sodium Glucose Transporter Inhibitors (SGLT2is)

Several SGLT2is have been evaluated in T1DM, including canagliflozin, dapagliflozin, empagliflozin and sotagliflozin. On the basis of Phase 3 clinical trials, dapagliflozin was licensed for use in T1DM in Europe, before its manufacturer voluntarily removed the indication late in 2021.[12] The U.S. Food and Drug Administration (FDA) did not approve an application for sotagliflozin to be licensed for use in T1DM.

A meta-analysis of randomized clinical trials of SGLT2is used as adjuncts to insulin in T1DM showed similar reductions in A1c and insulin dose to those with metformin and GLP-1RAs, with intermediate-level reductions in body weight (Table 1).[13] Reductions in blood pressure, LDL and triglyceride levels were also reported. Even in relatively small clinical studies, SGLT2is were clearly associated with an increased risk for DKA (2.5–5% in 26-week studies), albeit they were invariably associated with a precipitating factor, as well as with genital tract infections.[13] The EASE trials were able to reduce the risk of DKA by including a low-dose arm using empagliflozin at 2.5 mg daily. This resulted in lower efficacy for reductions in A1c and insulin dose, with no significant reduction in body weight versus 10 mg or 25 mg dosing.[14] SGLT2i use was also associated with more time in range and less glucose variability.[14,15]

Summary and Interpretation

There is clear evidence that the addition of NIAHAs can have beneficial effects for glycemic control, without the adverse effects of body weight gain and/or hypoglycemia, which would be expected with insulin. Their adverse effects (AEs) are generally predictable and manageable (GI AEs with metformin and GLP-1RAs; and genital infections with SGLT2is). The risks of DKA with SGLT2is are finite but significant and should prompt a pause, particularly because of the dissociation between hyperglycemia and ketosis. However, the question of why these agents have not been licensed for use in T1DM in Canada remains.

This may be due, in part, because of the current glucocentric focus, such that the reductions in HbA1c are perceived to be marginal and of limited clinical significance. However, a key oversight is to view the "small, incremental" reductions in body weight, insulin dose and A1c as independent parameters. Clearly, they are interdependent; however, the changes seen with the addition of NIAHAs run counter to what would normally be expected. An intervention that lowers A1c while reducing both body weight and insulin dose is surprising, but highly valued by patients. This may be reflected in the improvements in patient quality of life and treatment satisfaction observed in several clinical studies but has been most striking in terms of the strong preference of clinical trial participants to remain on active drug at the conclusion of clinical trials of NIAHAs—note that this is a personal observation.

Overall, there appears to be little or no increase in hypoglycemia with these NIAHAs. Given the nature of blinded trials, which may have included a treat-to-target design, it may be easier to avoid hypoglycemia with NIAHAs in clinical practice as there is no placebo, and proactive adjustments to insulin doses can be made.

Apart from the treatment effects on A1c is the desire to avoid complications and mortality. It is striking that metformin seems to have some cardiometabolic benefits that may be relevant to atherosclerosis. The trials of GLP-1RAs and SGLT2is have not been of sufficient duration to provide any clear information about their benefits. An extremely important question, however, is whether SGLT2i may have renal benefits in T1DM subjects with diabetic nephropathy. A Canadian-led study (SUGARNSALT) has been designed to answer that question.[16]

Conclusion

Patients with T1DM desire and deserve more than simply improved A1c. Mean blood glucose does not adequately reflect how people feel. Blood glucose variability, within and between days, is a major frustration and impediment which is better captured by continuous glucose monitoring (CGM). Therefore, it is intriguing that both GLP-1RAs and SGLT2is appear to be associated with more time in range and less glucose variability. Greater attention should be paid to evaluating patient preferences and quality of life in future studies of NIAHAs in T1DM, using more specific instruments and/or qualitative methods.

Practical Next Steps

Clinical trials provide important information about the safety and efficacy of new agents. Often, they are designed to be broadly generalizable, but this may overlook the fact that not all patients will benefit equally. Therefore, an individualized, patient-centred approach seems optimal from both an intellectual and inter-personal perspective. Selective use of NIAHAs in individuals struggling with weight gain, insulin resistance and/or difficulty reaching glycemic targets would be an obvious place to begin. Weighing the risks of DKA in individuals and providing education and tools for sick day management is important prior

to initiating an SGLT2i. Adopting these agents for a therapeutic trial, perhaps sequentially, could usefully inform shared decision-making, while access, coverage and side effects may limit therapeutic choices. While T1DM patients do not have a choice about whether or not to continue taking insulin, they can make choices about whether or not continuing to take an NIAHA is worth it to them, assuming that their physician administered it as a trial. While the Canadian Agency for Drugs and Technologies in Health (CADTH) states that "Marketing of off-label uses is prohibited," it also notes that "Off-label prescribing is allowed, and necessary in some cases."[17] NIAHAs are not licenced for use in T1DM; however, there is clear evidence from multiple clinical trials that they can deliver meaningful results. This supports careful and judicious off-label prescribing with the objective of delivering optimal care to individuals with T1DM.

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