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Adjunctive Therapy with Pramlintide Lowers HbA1c without Concomitant Weight Gain and Increased Risk of Severe Hypoglycemia in Patients with Type 1 Diabetes Approaching Glycemic Targets

Abstract

Aims: In long-term clinical trials in patients with type 1 diabetes spanning a wide range of HbA1c, addition of pramlintide to existing insulin regimens led to reductions in HbA1c that were accompanied by weight loss and no increase in overall severe hypoglycemia event rates. Given that weight gain and increased hypoglycemia risk contribute to the difficulty of attaining HbA1c targets (< 7%), the question arose whether pramlintide could benefit patients approaching, but not reaching glycemic targets with insulin alone. To address this question, we conducted a pooled analysis from 3 long-term clinical trials, including all patients with an entry HbA1c between 7.0% and 8.5%. **Methods:** Within the subset of patients with an entry HbA1c between 7.0% and 8.5% (approximately 28% of all patients enrolled in the 3 studies), 196 were treated with placebo + insulin (baseline HbA1c 7.9 ± 0.4%, body weight 76.0 ± 14.3 kg [mean ± SD]) and 281 with pramlintide + insulin (baseline HbA1c 7.9 ± 0.4%, body weight 75.4 ± 13.1 kg). Endpoints included placebo-corrected changes from baseline to week 26 in HbA1c, body weight, and the event rate of severe hypoglycemia. **Results:** Adjunctive therapy with pramlintide resulted in significant reductions in HbA1c and body weight from baseline to week 26 (0.3% and 1.8 kg, placebo-corrected treatment differences, respectively, both $p \leq 0.0009$). These changes occurred without an increase in the overall risk of severe hypoglycemia (1.40 pramlintide vs. 1.86 placebo, events/patient-year of exposure). **Conclusions:** Addition of pramlintide to insulin therapy may help patients with type 1 diabetes who are approaching, but not yet reaching, glycemic targets with insulin alone to achieve further reductions in HbA1c without concomitant weight gain and increased risk of severe hypoglycemia.

Key words
HbA1c · pramlintide · type 1 diabetes · glycemic targets

Introduction

For over 80 years, insulin replacement therapy has been the primary pharmacological treatment for type 1 diabetes. Despite advances in insulin formulation and delivery, such as the development of rapid- and long-acting insulin analogs (Bolli et al., 1999) and continuous subcutaneous insulin infusion (CSII) (Felig et al., 1979), only a small proportion of patients with type 1 diabetes achieves near-normalization of HbA1c levels and most achieve HbA1c levels no better than 8% (Klein et al., 1996; Nathan et al., 1996; Booth et al., 2002). Efforts to achieve target HbA1c levels (< 7% or < 6.5%, according to the American Diabetes Association [ADA] and the American Association of Clinical Endocrinologists [AACE] guidelines, respectively) (American Diabetes Association, 2003; American Association of Clinical Endocrinologists, 2002) by intensifying insulin therapy are impeded by a failure to re-

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store physiological insulin and glucose kinetics (especially during the postprandial period) (Weyer et al., 2001), undesired weight gain (DCCT Research Group, 1988; Purnell et al., 1998; DCCT Research Group, 2001), and most notably, an increased risk of severe hypoglycemia (DCCT Research Group, 1991; DCCT Research Group, 1993; Cryer, 1994; DCCT Research Group, 1997). In the Diabetes Control and Complications Trial (DCCT), the risk of severe hypoglycemia increased exponentially as HbA1c values decreased towards near-normal levels (DCCT Research Group, 1997), thus confirming clinical experience that the limitations of insulin therapy become increasingly evident as patients approach glycemic targets.

Amylin is a second β-cell hormone that is normally co-secreted with insulin in response to meals and, like insulin, is absolutely deficient in patients with type 1 diabetes (Koda et al., 1992). Amylin complements the effects of insulin in postprandial glucose homeostasis by regulating the rate of glucose inflow into the circulation to better match the rate of insulin-mediated glucose disposal (Weyer et al., 2001; Young, 1997). This is achieved both by a suppression of nutrient-stimulated glucagon secretion, often seen in diabetes (Gedulin et al., 1997), as well as a slowing of gastric emptying (Young et al., 1995). Pramlintide is an analog of amylin recently approved in the United States to be given at mealtimes as an adjunct to mealtime insulin therapy in patients with type 1 or type 2 diabetes who have failed to achieve desired glucose control despite optimal insulin therapy or insulin therapy with or without concurrent sulfonylurea agent and/or metformin, respectively (SYMLIN® Prescribing Information, 2005). Short-term clinical studies in patients with type 1 diabetes have shown that mealtime amylin replacement via subcutaneous injection of pramlintide, in addition to mealtime insulin injections, improves postprandial hyperglucagonemia (Nyholm et al., 1999; Fineman et al., 2002), slows the rate of gastric emptying (Kong et al., 1997; Vella et al., 2002), and, concomitantly, improves postprandial glucose excursions (Nyholm et al., 1999; Kolterman et al., 1995; Weyer et al., 2003). Three long-term clinical studies in patients with type 1 diabetes have shown that the addition of pramlintide to pre-existing insulin regimens facilitates a further improvement of overall glycemic control (HbA1c reduction) without the long-term increases in body weight and severe hypoglycemia risk that are typically seen when glycemic control is improved with insulin alone (Fineman et al., 1999; Ratner et al., 2004; Whitehouse et al., 2002). Patients included in these long-term studies were representative of a type 1 diabetes population in the general healthcare setting, with entry HbA1c levels ranging from 7% to 13% (Fineman et al., 1999; Ratner et al., 2004; Whitehouse et al., 2002).

Given that weight gain and increased hypoglycemia risk contribute to the difficulty of attaining HbA1c targets (< 7%), the question arose whether pramlintide could benefit patients approaching, but not reaching glycemic targets with insulin alone. To address this question, we conducted a pooled analysis from 3 long-term clinical trials, including all patients with an entry HbA1c between 7.0% and 8.5%.

Subjects and Methods

Patients and study design

Patients who participated in the original studies had type 1 diabetes requiring insulin treatment for a minimum of 1 year and had their diabetic status verified by one or more of the following criteria: C-peptide ≤ 1.0 ng/mL, documented history of diabetic ketoacidosis consistent with type 1 diabetes, or previously documented islet cell immune marker positive (islet cell antibody or other antibodies) to islet antigens. The HbA1c range of 7.0% to 8.5% was chosen because it reflected those patients who were in good but still not optimal glycemic control.

The designs of the 3 long-term, randomized, double-blind, placebo-controlled, studies included in this pooled analysis have previously been described in detail (Fineman et al., 1999; Ratner et al., 2004; Whitehouse et al., 2002). In brief, all 3 studies utilized an add-on design, i.e., pramlintide or placebo (injected subcutaneously TID or QID prior to the major meals) were added to pre-existing insulin regimens. All 3 studies had the same efficacy and safety endpoints (see below), with repeated assessment of HbA1c, body weight, total daily insulin doses (recorded in subject diaries), and severe hypoglycemic events (defined according to DCCT criteria [DCCT Research Group, 1991; DCCT Research Group, 1993; DCCT Research Group, 1997]: any event requiring administration of glucagon, glucose, or the assistance of another person or hospitalization) throughout the study. The 3 studies differed in length (2 studies of 52 weeks' duration and 1 study of 26 weeks' duration) and in the pramlintide dosing regimens used (30 or 60 µg given TID or QID).

For the present analysis, we pooled all 3 studies and included data from all patients who had been randomized to pramlintide (30 or 60 µg given TID or QID), and who had an HbA1c value between 7.0% and 8.5% at study entry.

Endpoints

Endpoints included the change from baseline to week 26 in HbA1c, body weight, insulin use, and the event rate per subject year of severe hypoglycemia.

Statistical methods

All efficacy and safety analyses were performed on the intent-to-treat (ITT) population (all randomized subjects with an entry HbA1c between 7.0% and 8.5% who received at least one dose of study medication). HbA1c and body weight changes between pramlintide and placebo groups were measured descriptively (mean, median, minimum, maximum, standard deviation, and standard error) and parametrically (ANOVA). Bolus injections for patients using continuous subcutaneous insulin infusion (CSII) were included in the number of daily injections statistic. The rate of severe hypoglycemia (based on calculations used in the DCCT [DCCT Research Group, 1997]) was expressed as event rate per subject-year and was calculated as: (total number of events for all subjects in a treatment regimen) divided by (total number of subject-years of observation for all subjects in a treatment).

Table **1** Demographics and baseline characteristics

	Placebo (pooled analysis)		*Pramlintide (pooled analysis)*	
n (ITT population)	196		281	
*Age, y**	42 ± 13		41 ± 12	
Sex M/F, %	55/45		50/50	
Race white/other, %	94/6		97/3	
*Body weight, kg**	76.0 ± 14.3		75.4 ± 13.1	
*BMI, kg/m²**	25.8 ± 4.0		25.7 ± 3.6	
*Diabetes duration, y**	19 ± 11		18 ± 10	
– *median duration (minimum, maximum), y*	19.0 (1.1, 57.0)		17.0 (1.0, 50.1)	
HbA1c, %	7.9 ± 0.4		7.9 ± 0.4	
*Total daily insulin dose, U**	48 ± 21		50 ± 27	
Number of daily insulin injections, %				
– *1*	2		2	
– *2*	25		23	
– *3*	63		68	
– *continuous subcutaneous insulin infusion, CSII*	10		7	
Types of insulin, %	week 0	week 26	week 0	week 26
– *short-acting only*	12	11	11	13
– *long-acting only*	4	4	8	11
– *short- & long-acting*	84	85	81	76

* Data are mean ± SD

Results

Patient disposition and baseline demographics

Of the 1717 patients enrolled in the 3 studies, 477 (approximately 28%; 281 pramlintide patients, 196 placebo patients) had entry HbA1c levels between 7.0% and 8.5% (exclusive), and were randomized to 1 of the 4 selected dosage regimens (30 or 60 µg TID or QID, or placebo). The 2 treatment groups were well-matched with respect to demographics and baseline characteristics (Table **1**). The vast majority of patients were on multiple injections of short- and/or long-acting insulin. The mean entry HbA1c was < 8% and the average BMI was > 25 kg/m² (the cutoff for overweight, according to WHO criteria) (World Health Organization, 2000). With the exception of entry HbA1c, key baseline characteristics of the present subgroup, including mean diabetes duration, were similar to those of the overall population studied in the original studies (Fineman et al., 1999; Ratner et al., 2004; Whitehouse et al., 2002).

Of the placebo-treated patients, 20% withdrew prior to week 26, with the two major reasons being withdrawal of consent (6%) and adverse events (5%). By comparison, 33% of the pramlintide-treated patients withdrew prematurely; again withdrawal of consent (8%) and adverse events (17%) were the most common reasons.

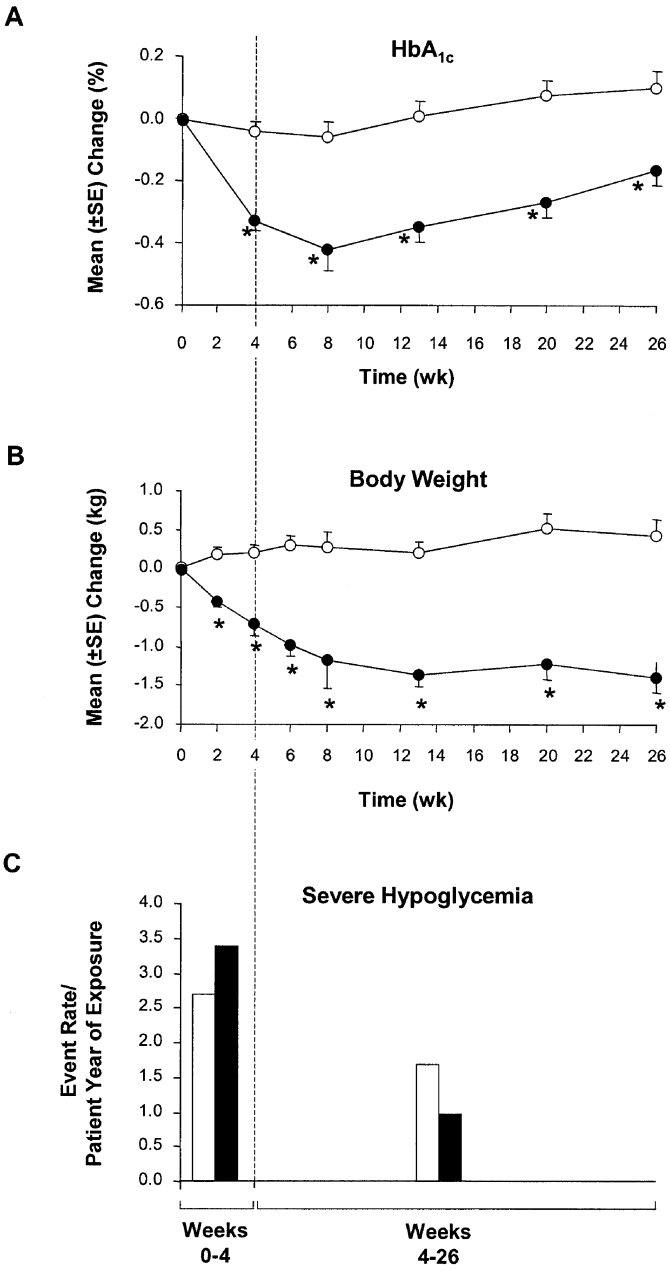

Fig. **1 A** to **C** Mean (± SE) change in HbA1c (**A**) and body weight (**B**) from baseline to week 26. Open circles represent placebo + insulin group, filled circles represent pramlintide + insulin group. Asterisks indicate significant difference from placebo, $p < 0.005$. Event rate for severe hypoglycemia from weeks 0 to 4 and weeks 4 to 26 (**C**). Open bars represent placebo + insulin group, filled bars represent pramlintide + insulin group.

HbA1c

Pramlintide-treated patients achieved a significant decrease in HbA1c compared to placebo-treated patients. The change in HbA1c was significant from week 4 through week 26 (Fig. **1 A**), whether calculated as placebo-corrected (– 0.3% at week 26, $p = 0.0009$) or as change from baseline (– 0.16% at week 26, $p = 0.0009$). The placebo-corrected HbA1c reduction of 0.3% was similar in magnitude to those observed in the original studies which included less well controlled subjects (– 0.58%, $p = 0.0001$ [Whitehouse et al., 2002]; – 0.2%, $p = 0.007$ [Fineman

et al., 1999], and – 0.41% [60 µg TID] and – 0.39% [60 µg QID], $p < 0.05$ [Ratner et al., 2004]).

At week 26 in the pooled analysis, 27 patients (9.6%) in the pramlintide-treated group and 14 patients (7.1%) in the placebo-treated group achieved an HbA1c < 7.0%.

Body weight

Along with the greater reduction in HbA1c, pramlintide-treated patients experienced a significant decline in weight compared to placebo-treated patients. The placebo-corrected weight reduction was significant ($p \leq 0.0001$) from week 4 onward and averaged 1.8 kg at week 26 (Fig. **1 B**).

The placebo-corrected weight reduction of 1.8 kg was similar in magnitude to those observed in the original studies, which included subjects with HbA1c > 8.5% (– 1.6 kg, $p \leq 0.0001$ [Whitehouse et al., 2002]; – 1.7 kg, $p < 0.05$ [Fineman et al., 1999], and – 2.0 kg [pramlintide 60 ug TID] and – 1.7 kg [pramlintide 60 ug QID], both $p < 0.05$ [Ratner et al., 2004]).

Insulin use

The mean total daily insulin use declined by approximately 4% in the pramlintide group and increased by approximately 3% in the placebo group. These shifts occurred despite the fact that the study design of all 3 trials encouraged patients to maintain a stable insulin regimen.

Severe hypoglycemia

Overall (0 to 26 weeks), the event rate per subject year of severe hypoglycemia in the pramlintide group was somewhat lower than in the placebo group (1.40 pramlintide vs. 1.86 placebo). While the event rate of severe hypoglycemia during the initial 4 weeks was generally high for both the pramlintide and placebo groups, it subsequently declined to a greater extent in the pramlintide- than in the placebo-treated group (Fig. **1 C**). The overall severe hypoglycemia event rates per subject year of 1.40 (pramlintide) and 1.86 (placebo) were slightly higher than those observed in the original studies, which included less well controlled subjects (Whitehouse et al., 2002; Fineman et al., 1999; Ratner et al., 2004).

Safety

Pramlintide treatment was generally well-tolerated. As previously reported, there was no evidence of cardiovascular, hepatic, or renal toxicity and no changes in laboratory safety parameters or ECG variables were observed (Fineman et al., 1999; Ratner et al., 2004; Whitehouse et al., 2002). There were also no differences in fasting lipids, heart rate, or systolic or diastolic blood pressure between the pramlintide and placebo groups. The only treatment-emergent adverse events with an incidence > 10% and a 2-fold greater incidence among pramlintide- vs. placebo-treated patients were nausea and anorexia (Table **2**). Most nausea events were mild to moderate in intensity, occurring within the first 4 weeks of therapy and dissipating over time (Table **2**).

Table **2** Treatment-emergent adverse events with an incidence > 10% and the incidence in the pramlintide group at least double that of the placebo group (Population: Intent-to-treat)

	Placebo		*Pramlintide*	
	all events	*severe events*	*all events*	*severe events*
	n (%)	*n (%)*	*n (%)*	*n (%)*
Nausea (0 – 26 weeks)	20 (10)	2 (1)	122 (43)	21 (8)
– *0 – 4 weeks*	11 (6)	2 (1)	113 (40)	19 (7)
– *4 – 26 weeks*	11 (6)	0 (0)	25 (9)	2 (1)
Anorexia (0 – 26 weeks)	3 (2)	0 (0)	45 (16)	5 (2)

Discussion

A fundamental obstacle in the pursuit of optimal glycemic control in patients with type 1 diabetes is that reductions in HbA1c via intensification of insulin therapy alone are typically accompanied by a significant increase in the risk of severe hypoglycemia (DCCT Research Group, 1991; DCCT Research Group, 1993; Cryer, 1994; DCCT Research Group, 1997), as well as considerable weight gain (DCCT Research Group, 1988; Purnell et al., 1998; DCCT Research Group, 2001). These clinical shortcomings of insulin therapy become increasingly apparent as HbA1c values advance toward the near-normal range and may therefore be particularly limiting in patients who are approaching, but not quite reaching, glycemic targets (DCCT Research Group, 1993; Cryer, 1994; Edelman and Weyer, 2002; Buse et al., 2002).

The results of the present analysis indicate that the addition of pramlintide to insulin therapy in patients with type 1 diabetes who are in fair, but still suboptimal, glycemic control (HbA1c 7.0% to 8.5%) facilitates a significant reduction in HbA1c without increases in body weight or overall risk of severe hypoglycemia.

The magnitude and durability of the observed HbA1c reduction are approximately equivalent to those observed in the original studies (Fineman et al., 1999; Ratner et al., 2004; Whitehouse et al., 2002). Because the overall study population in these trials had a mean entry HbA1c of approximately 9%, and included patients with entry HbA1c values as high as 13%, it was uncertain whether the observed HbA1c reduction with pramlintide was also present in those patients who were already in fair glycemic control at study entry when treated with insulin alone. The present results indicate that pramlintide treatment can lead to a further glycemic improvement in this subgroup of patients. Thus, while the mean HbA1c in both pramlintide and placebo groups at study entry was already below 8%, pramlintide-treated patients achieved a significant reduction in HbA1c, above and beyond that achieved with insulin alone (placebo group) (Fig. **1**). While the mean HbA1c value reached a nadir after 8 weeks and gradually increased thereafter in both groups, a significant place-

bo-corrected treatment difference was maintained throughout the study.

Although the long-term trials included in the present analysis did not assess fasting and postprandial glucose concentrations, other studies indicate that pramlintide's effect on HbA1c is predominantly, if not exclusively, mediated by a reduction in postprandial glucose excursions (Nyholm et al., 1999). This is a highly desirable attribute, not only because excessive postprandial glucose excursions are very common even in intensively treated, well-controlled patients with type 1 diabetes (Kaufman et al., 2001; Boland et al., 2001), but also because a smoothing of postprandial glucose swings may enable patients to more aggressively, and safely, pursue fasting glucose targets, such as by adjusting their basal insulin regimen.

It is important to note that most patients in our analyses were already using intensive, multiple daily insulin regimens at the time of study entry. Since insulin regimens and types of insulin used remained stable throughout the study and total daily insulin dose, if anything, decreased in the pramlintide- compared to the placebo-treated patients, it can be concluded that pramlintide treatment facilitated an additional glycemic improvement beyond that achieved with insulin alone.

As previously observed in the individual clinical trials (Fineman et al., 1999; Ratner et al., 2004; Whitehouse et al., 2002), pramlintide-treated patients approaching glycemic targets experienced a mean reduction in body weight, rather than the weight gain typically seen when glycemic control is improved with insulin alone. This finding is clinically relevant for several reasons. First, the patients' mean BMI was already well within the overweight range at study entry. Second, it has repeatedly been reported that a large proportion of patients with type 1 diabetes fail to intensify insulin therapy, and even reduce and omit insulin injections, for fear of weight gain (Bryden et al., 1999). Third, in the DCCT, weight gain with intensified insulin therapy was accompanied by clinically significant deteriorations of cardiovascular risk factors, including proportionate increases in systolic and diastolic blood pressure, as well as serum triglyceride and LDL cholesterol concentrations (Purnell et al., 1998; Purnell and Weyer, 2003). The mechanism underlying the observed weight reduction with pramlintide has not yet been fully elucidated; however, there is increasing evidence from rodent studies that amylin's effects include a reduction in food intake and body adiposity (Rushing et al., 2000; Rushing et al., 2001). Consistent with these non-clinical findings are the results of a recent randomized, double-blind, placebo-controlled cross-over study, in which preprandial injection of pramlintide elicited a significant, ~20% reduction in ad-libitum food intake in insulin-treated patients with type 2 diabetes (Chapman et al., 2005). Although food intake was not an outcome measure of the long-term studies included in this analysis, it is interesting to note that the apparent increase in the incidence of anorexia with pramlintide-treatment (Table **2**) was, in part, attributable to reports of increased satiety, reduced appetite, and fullness.

Another, well-recognized, DCCT finding is that improvement of glycemic control with insulin therapy is associated with a considerable increase in severe hypoglycemia risk (DCCT Research Group, 1991; DCCT Research Group, 1993; Cryer, 1994; DCCT Research Group, 1997). Based on the DCCT data, it would be predicted that patients who achieve an HbA1c of 7% with either conventional or intensive insulin therapy have an approximately 50% to 100% higher risk of severe hypoglycemic events than those who achieve an HbA1c of 8% with either regimen (DCCT Research Group, 1991). It was therefore an important finding that the reduction in HbA1c with pramlintide treatment was not associated with an increase in the overall event rate of severe hypoglycemia compared to placebo treatment. In some of the individual studies, pramlintide treatment was associated with a transient increase in the event rate of severe hypoglycemia during the first 4 weeks (Whitehouse et al., 2002). Interestingly, in the present pooled analysis, in patients who were already in fair glycemic control at study entry, the event rate of severe hypoglycemia during the first 4 weeks was comparable between the pramlintide and placebo groups. Nevertheless, regular blood-glucose self-monitoring and judicious insulin dose adjustment, such as appropriate reductions of preprandial insulin doses, should help avoid hypoglycemia when initiating pramlintide therapy in fairly well-controlled patients. Beyond the initial 4 weeks, the event rate of severe hypoglycemia for pramlintide-treated patients was, if anything, somewhat lower than in placebo-treated patients, despite the fact that a greater reduction in HbA1c was maintained. Although the explanation for this finding is currently unknown, it is interesting to note that pramlintide has been shown to reduce excessive 24-hour glucose fluctuations in patients with type 1 diabetes intensively treated with insulin pumps (Levetan et al., 2003).

In the interpretation of the aforementioned findings, it is noteworthy that the withdrawal rates and baseline characteristics, with the exception of glycemic control, of the present subgroup were not dissimilar from those observed in the original protocols. Also, for the present analysis, different pramlintide dosing regimens were pooled and hence, no conclusions on the dose-response relationship for the pramlintide-mediated reduction in HbA1c and weight can be drawn. However, detailed information on various pramlintide dosing regimens is provided in the publication of the original studies (Whitehouse et al., 2002; Fineman et al., 1999; Ratner et al., 2004).

In summary, the results of the present analysis indicate that the addition of pramlintide to insulin therapy facilitates a significant further reduction in HbA1c without increases in body weight or the overall event rate of severe hypoglycemia in patients with type 1 diabetes who are in fair, but still suboptimal, glycemic control. Pramlintide may therefore be a valuable adjunct to insulin therapy that may help patients with type 1 diabetes who are approaching, but not yet reaching HbA1c goals, to safely achieve further improvements in glycemic control.

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