REVIEW ARTICLE

Role of premixed insulin analogues in the treatment of patients with type 2 diabetes mellitus: A narrative review

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Abstract

Because of the progressive nature of type 2 diabetes mellitus (T2DM), insulin therapy will eventually become necessary in most patients. Recent evidence suggests that maintaining optimal glycemic control by early insulin therapy can reduce the risk of microvascular and macrovascular complications in patients with T2DM. The present review focuses on relevant clinical evidence supporting the use of premixed insulin analogues in T2DM when intensifying therapy, and as starter insulins in insulin-naïve patients. Our aim is to provide relevant facts and clinical evidence useful in the decision-making process of treatment selection and individualized treatment goal setting to obtain sustained blood glucose control.

Keywords: glycated hemoglobin, HbA1c, premixed insulin analogue, type 2 diabetes mellitus.

Introduction

With an increase in obesity and the adoption of a Western-like lifestyle in developing countries, the prevalence of type 2 diabetes mellitus (T2DM) is increasing rapidly worldwide, with T2DM accounting for approximately 90% of patients with diabetes.[1] In addition, the worldwide increase in obesity in younger age groups (children and adolescents) has triggered an increasing tendency for an earlier onset of T2DM.[2] These patients will be exposed to T2DM for a longer time and will eventually become severely insulin deficient, at which time they will require insulin-replacement therapy.[3]

Although many patients can be managed initially with diet and oral medication, the steady decline in β-cell function,[3] regardless of the treatment used, ultimately necessitates the start of insulin therapy. Unfortunately, many patients fear the intensification of treatment; hence, many healthcare providers are reluctant to start insulin, and such treatment may be postponed for several months or even years.[4] Suboptimal choice of treatment and/or dosage for fear of inducing adverse events once oral blood glucose (BG)-lowering agents have failed is very common in clinical practice.[4,5] Therefore, we conducted an extensive review focusing on relevant evidence supporting the use of premixed insulins in T2DM when intensifying therapy and as starter insulin in insulin-naïve patients.

A literature search was conducted on Medline, Embase, and PubMed using the search terms "type 2 diabetes", "insulin", "premixtures", "insulin analogues", "insulin-naïve", "glycemic control", and "glycemic target" as far back as the 2000. The search was restricted to any article or abstract in English, per title reporting any information related to insulin analogue premixtures in patients with T2DM who did not achieve glycemic targets with oral therapy or basal insulin. Citations, including reviews, meta-analyses, and clinical trials, were screened and chosen depending on their relevance to the present review. References from these sources were also searched for relevant publications. Because there were not enough data to perform a meta-analytical review, we included a comprehensive description of the main results from the available data from the publications collected.

Glycemic targets

The UK Prospective Diabetes Study (UKPDS), which compared intensive BG treatment (insulin and sulfonylureas) with conventional treatment in patients with

T2DM, showed that intensive glycemic control from disease onset significantly reduces the rate of microvascular complications (retinopathy, nephropathy, and/or neuropathy).[6] In the 10-year follow-up to this study (the UKPDS legacy effect), the microvascular risk reduction continued, with significant reductions in the risk of myocardial infarction and death from any cause.[7]

Studies that assessed the effects of intensive treatment to reduce cardiovascular disease showed less beneficial effects. For example, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial tested the effect of intensive therapy (targeting glycated hemoglobin [HbA1c] levels <6%) versus standard glycemic control (targeting HbA1c levels from 7% to 7.9%) on cardiovascular disease (CVD) events.[8] That study was terminated after a mean follow-up of 3.5 years given the increased all-cause and CVD-related mortality. The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE)[9] and the Veterans Affairs Diabetes Trial (VADT)[10] reported no increase in CVD-related mortality, but no benefit of intensive therapy on macrovascular outcomes. However, these studies intensified treatment in patients who already had a long duration of diabetes and, in many cases, prevalent heart disease. Indeed, a post hoc analysis of the VADT showed beneficial effects of intensified insulin treatment on CVD, especially in those patients with a short duration of disease or who were free of CVD at baseline.[11]

Current treatment algorithms and guidelines recommend dose titration, changing interventions or regimens, and goal revising when treatment targets are not being met.[12–16] They also concur that target goals need to be individualized for specific clinical needs, clinical characteristics, and psychosocial factors because not all patients have benefited from stringent glycemic targets. Glycemic targets can be more demanding for younger patients without macrovascular disease (<45 years of age, HbA1c ≤6.5%) and more moderate when treating older patients with established macro- and microvascular complications (>75 years of age, HbA1c ~8%).[15,17]

What type of insulin are physicians in different countries using as starter insulin therapy?

Despite current guidelines, practices concerning insulin treatment vary widely among countries. Results from the INSulin TItration–GAining An understanding of Type 2 diabetes burden in Europe (INSTIGATE) observational study indicated that physicians in Germany often begin intensive insulin treatment at an early disease stage in newly diagnosed patients instead of favoring oral

BG-lowering agents.[18] German physicians favored the use of short-acting insulin as starter insulin with a shift toward basal-bolus regimens at 6 months. In France and Spain, the most common insulin starter was long- and/or intermediate-acting insulin, whereas long- and/or intermediate-acting or premixed formulations were used most commonly in Greece and the UK.[18] The treatment regimens used across the different countries were consistent with local guidelines with very little shift to different regimens during the study period. The largest mean decrease in HbA1c (–2.3%) across the observed countries was accomplished in Germany, which was the only country to report HbA1c levels below 7%. Interestingly, the more intensive therapy used in Germany was not associated with higher self-reporting of hypoglycemia. Another interesting aspect of this study is the strong bias towards certain treatments that are not supported by specific aspects of lifestyle, such as local eating patterns. For example, Spain resorts to using basal insulin (long- and/or intermediate-acting component) as a starter regimen.[18]

Beginning insulin therapy in patients with T2DM

When to start insulin therapy

Patients with T2DM and long-standing disease will ultimately require treatment intensification with insulin alone or in combination with oral BG-lowering agents. Physicians should consider initiating insulin therapy in any given patient whose HbA1c remains above target despite maximal oral or non-insulin injectable therapy for a period of 3–6 months.[13–16]

The DURAbility of Basal versus Lispro mix 25 insulin Efficacy (DURABLE) trial included patients with T2DM whose oral BG-lowering agents failed and compared basal versus lispro mix 25 starter insulins.[19,20] The study found that patients with lower baseline HbA1c values in both treatment groups were most likely able to achieve and maintain the study glycemic target (HbA1c <7%).[19,20] This finding suggests that early insulin treatment may be important in maintaining HbA1c targets. It is also important to consider that, even though more intensified regimens have a possible beneficial effect on HbA1c and therefore on the onset of complications, intensified regimens may also have negative effects, such as greater weight gain, hypoglycemia, and hyperinsulinemia.

How to choose between basal and premixed insulin therapies to start treatment

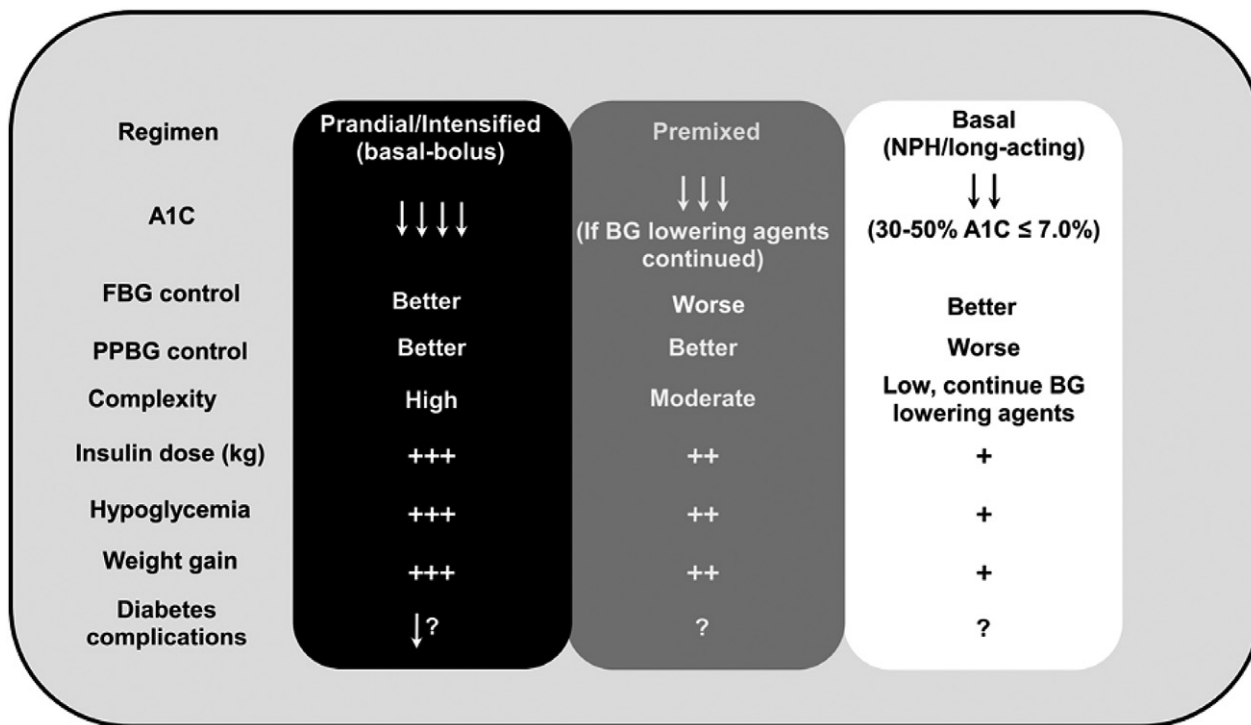There are three types of starter insulin regimens that can be used depending on patients' lifestyle patterns and

Figure 1 Comparison of the advantages and disadvantages of the different insulin regimens available.[15,17,23] Many starter regimens need intensification. More intensified regimens may have beneficial effects on A1C, and therefore on diabetes complications, but may also have negative effects, such as body weight gain, hypoglycaemia, and hyperinsulinaemia. The figure shows a comparison of the insulin regimens most commonly used in terms of efficacy outcomes, ease of use, dosage, adverse effects and whether it is known that they reduce diabetes complications. This figure reflects the interpretation of the authors and the references cited in the figure title. A1C, glycated hemoglobin; BG, blood glucose; FBG, fasting blood glucose; NPH, neutral protamine Hagedorn; PPBG, postprandial blood glucose; ↓↓↓↓, decrease; ↓↓↓, moderate decrease; ↓↓, slight decrease; +++, high; ++, moderate; +, low; ?, unknown; ↓?, low or unknown.

needs and the clinicians' regular practice: basal only, basal and prandial (with premixed insulin or self-mixed insulin), or a prandial-only regimen. At the beginning of therapy, all three regimens will enable patients to achieve glycemic targets,[21] but owing to the progressive nature of T2DM, ultimately both basal and prandial insulin will be needed to maintain HbA1c levels within the target range[22] (Fig. 1). As observed in the DURABLE trial, the addition of a short-acting insulin analog (as a component of premixed therapy), which can compensate for meal-related insulin secretory deficits, may be useful in patients with elevated postprandial BG.[19,20] Therefore, when choosing starting insulins, elevated postprandial glucose may be useful in guiding treatment selection and can help identify patients in need of treatment intensification.[23]

Basal-bolus insulin is the most physiological approach to insulin therapy initiation.[12–16] It can be adjusted independently to provide both basal and prandial coverage, but it requires strict and frequent BG self-monitoring, and patients need to be highly capable of self-management.

Patients also need to be strongly motivated to accept this multiple daily injection approach.

The basal insulin only regimen is simple and convenient because it only involves one basal insulin injection daily and limited BG monitoring.[24] Thus, it is easier to motivate patients to adhere to this regimen. The downside is that because it does not provide postprandial glycemic control, this regimen often fails to achieve and maintain target levels of HbA1c during the course of the disease and patients will eventually require greater daily insulin doses and treatment intensification to more complex insulin regimens.[22]

Postprandial coverage requires the addition of rapid-acting insulin to basal insulin. To avoid free mixing, pharmaceutical companies have developed premixed insulin analogues. These consist of a single formulation that contains both the basal and prandial rapid-acting component. Premixed insulin analogues can provide both basal and postprandial coverage starting with one injection. It has been demonstrated that premixed insulin analogues offer better postprandial glycemic

control than basal insulin used alone,[25] which is of proven importance in achieving HbA1c targets.[26] A recent meta-analysis concluded that greater HbA1c reductions can be achieved with premixed and prandial insulin compared with basal insulin.[27] In addition, there were no differences between premixed–prandial and basal insulin in severe hypoglycemic events, and only minor hypoglycemic events were observed.[27] These results are in line with another recent systematic review in which Ilag et al.[23] found no difference between premixed and basal insulin in the frequency of nocturnal or severe hypoglycemia.

Premixed analogues can conveniently be administered twice daily directly before the meal. Physicians may recommend adding further injections depending on patients' individual needs.[28] When patients forget to administer the premixed analogues before the meal, they can still administer the corresponding dose soon after the meal without risk of hyperglycemia. Patients can also learn to adjust the dose depending on the amount of carbohydrates that will be consumed during a particular meal.[29]

Ilag et al. suggest that the intensive treatment ratio containing 50% of a basal component and 50% of a rapid-acting component can closely resemble normal physiologic insulin secretion.[23] Premixed insulin formulations commercially available today include biphasic insulin aspart 70/30 (70% insulin aspart protamine suspension, 30% insulin aspart [BIAsp 30], NovoMix™ 30, Novo Nordisk, Bagsvaerd, Denmark), insulin lispro mix 25 (25% insulin lispro, 75% insulin lispro protamine suspension [LM25], Humalog™ Mix25™, Eli Lilly and Company, Indianapolis, IN, USA), and insulin lispro mix 50 (50% insulin lispro, 50% insulin lispro protamine suspension [LM50], Humalog™ Mix50™, Eli Lilly and Company, Indianapolis, IN, USA).

In the Treating to Target in Type 2 Diabetes (4-T) trial,[21] patients randomized to BIAsp 30 or insulin aspart plus oral therapy had lower HbA1c levels but more weight gain and hypoglycemia after 1 year compared with those randomized to insulin detemir (Table 1). After 3 years, the improved glycemic control was generally maintained, but most patients required titration to more complex basal-bolus insulin regimens.[22] Of note, there were fewer serious adverse events and cardiovascular deaths in patients initially treated with insulin detemir compared with those initially treated with BIAsp 30 or insulin aspart, with the highest rate in patients in the prandial group.[22] Although these data suggest that the fast-acting component of BIAsp 30 may have contributed to these differences, the data cannot be fully evaluated because only a limited number of events were reported and results for individual events were not statistically significant.[22]

Premixed insulin analogues are a simplified and convenient alternative with a lower number of daily injections for patients with T2DM who cannot or who are not willing to use basal-bolus insulin.[30] This treatment approach is also suitable for patients who do not wish to or cannot count carbohydrates, or those who have consistent eating patterns and routine lifestyles.[29] Patients who have high baseline HbA1c values and elevated postprandial BG levels can also benefit from a premixed insulin regimen.[23] As with any insulin therapy, premixed insulin analogues have also proven useful as acute treatment in the case of severe hyperglycemia.[23]

When to switch from basal insulin therapy to premixed insulin therapy

Results from the PREFER study by Liebl et al. suggest that the choice between premixed insulin analogues or basal-bolus therapy should be individualized for patients in whom BG lowering agents with or without basal insulin failed.[31] Patients already on basal insulin responded better and achieved better glycemic control with basal-bolus therapy, while premixed insulin analogues proved to be equally effective in insulin-naïve patients (Table 1).[31] Patients treated with one daily dose of basal insulin (neutral protamine Hagedorn [NPH], detemir, glargine), who have not achieved HbA1c target, and have postprandial BG above limits despite appropriate fasting BG levels may be transitioned to premixed insulin analogues. Patients treated with basal-bolus regimens who are non-compliant with self-monitoring and titration of multiple insulin doses can also benefit from a transition to premixed insulin analogues.

How to start a premixed insulin regimen: Dosage and titrations

As an insulin starter regimen in patients in whom oral BG-lowering agents have failed, the algorithm of Hirsch et al. recommends beginning treatment with 10 units LM25 twice daily (once before breakfast and once before dinner).[3] Based on the results of the DURABLE trial,[32] we suggest a less aggressive starting dose of 8 units (±4 units), depending on the patient's age, body weight, diet, and physical activity, to prevent hypoglycemic events. In the DURABLE trial, the majority of severe hypoglycemic events occurred during the first 12 weeks of the study, which corresponded to the insulin titration period. In another clinical trial involving patients with no response to two or more oral BG-lowering agents, the initial dose of LM50 was 10–12 units with dinner.[33] The evening dose was adjusted according to the BG at bedtime, and additional injections were added if BG targets were not attained after 4–12 weeks (BG before

Table 1 Comparator trials including premixed insulin analog

Reference	Study design/duration	Study treatment (no. randomized patients)	HbA1c (mean)	Fasting and postprandial SMPG or SMBG†	Hypoglycemia	Weight gain + or loss − (mean, kg)
Buse et al.[19]	R, OL, MC, P/24 weeks (prior OADs)	LM25 (n = 1045) vs glargine (n = 1046) Continuation of prior OADs (both arms)	Starting: 9.1% vs 9.0%; ending: 7.2% vs 7.3% (P = 0.005) Reduction from baseline to endpoint significantly greater for LM25 vs glargine (P = 0.005) Patients reaching target: <7%, 47.5% vs 40.3% (P < 0.001)	FPG: 134 vs 122 mg/dL (P < 0.001) PPPG: Breakfast 167 vs 172 mg/dL (P < 0.05) Lunch (NS)§ Dinner (evening meal) 163 vs 176 mg/dL (P < 0.001)	Episodes/patient per year Overall (mean at endpoint): 28.0 vs 23.1 (P = 0.007) Nocturnal (mean at endpoint): 8.9 vs 11.4 (P = 0.009) Severe (mean over entire study duration): 0.10 vs 0.03 (P = 0.167)	+3.6 vs +2.5 (P < 0.001)
Holman et al.[21]	R, OL, MC/52 weeks (prior metformin and/or SU)	BIAsp 30 (n = 235) vs insulin aspart (n = 239) vs insulin detemir (n = 234) Continuation of metformin and/or SUs (all arms)	Starting: 8.6% (BIAsp 30 and aspart) vs 8.4% (detemir); ending: 7.3% vs 7.2% vs 7.6% (BIAsp 30 vs aspart, P = 0.08; BIAsp 30 vs detemir, aspart vs detemir, P < 0.001) Reduction from baseline to 1 year greater for BIAsp 30 and aspart vs detemir (P-values NR) Patients reaching target: ≤7.0%, 41.7% vs 48.7% vs 27.8% (BIAsp 30 vs aspart, P = 0.08; BIAsp 30 vs detemir, aspart vs detemir, P < 0.001) ≤6.5%, 17.0% vs 23.9% vs 8.1% (BIAsp 30 vs aspart, P = 0.08, BIAsp 30 vs detemir, P = 0.001; aspart vs detemir, P < 0.001)	FPG (change from baseline [175 vs 173 vs 171 mg/dL] to 1 year): −45 vs −23 vs −59 mg/dL PPPG (change from baseline [229 vs 227 vs 223 mg/dL] to 1 year): −68 vs −83 vs −47 mg/dL (FPG and PPPG: BIAsp 30 vs aspart, BIAsp 30 vs detemir, aspart vs detemir, P < 0.001)	Events/patient per year (mean at 1 year): 5.7 vs 12.0 vs 2.3 (P-values NR)	+4.7 vs +5.7 vs +1.9 (BIAsp 30 vs aspart, P = 0.005; BIAsp 30 vs detemir, aspart vs detemir, P < 0.001)
Liebl et al.[31]	R, MC, MN, treat-to-target/26 weeks (up to two prior OADs with or without intermediate- or long-acting insulin)	BIAsp 30 (n = 178) vs insulin detemir/aspart (n = 541)	Starting: 8.40% vs 8.52%; ending: 7.17% vs 6.96% (baseline-corrected treatment difference [0.234%] in favor of detemir/aspart, P = 0.0052) Patients with prior basal insulin (HbA1c reductions): 0.75% vs 1.21% (P = 0.0129) Insulin-naïve patients (HbA1c reductions): 1.42% vs 1.69% (P = 0.106) Patients reaching target (≤7%): 50% vs 60%, P-value NR	FPG (baseline-corrected difference between treatment-group reductions): 0.21 mmol/L in favor of BIAsp 30 but NS (P = 0.345) PPPG (90 min PP) differences between treatment-group reductions in favor of detemir/aspart: Breakfast 0.63 mmol/L (P = 0.012) Lunch 1.81 mmol/L (P < 0.001) Dinner 0.76 mmol/L (P < 0.001)	Major: 0 vs 0.9% of patients (P-value NR) Minor (final 20 weeks of study): 0.037 vs 0.035 events/patient per week (P = 0.837) Nocturnal (minor, final 20 weeks of study): 0.010 vs 0.013 events/patient per week (P = 0.666)	+2.1 vs +2.4 (NS)
Rosenstock et al.[34]	R, OL, MC, noninferiority trial/24 weeks (prior glargine plus OADs)	LM50 (n = 187) vs glargine/insulin lispro lispro (n = 187) Continuation of OADs except SUs and glinides	Starting: 8.8% vs 8.9%; ending: 6.95% vs 6.78% (P = 0.021) Noninferiority of LM50 to glargine/lispro was not demonstrated based on a prespecified noninferiority margin of 0.3%. Patients reaching target: <7%, 54% vs 69% (P = 0.009) ≤6.5%, 35% vs 50% (P = 0.01)	FPG: 159 vs 147 mg/dL (P = 0.013) PPPG: Morning 174 vs 155 mmol/L (P = 0.002); all other time points (NS)	Episodes/patient per year (mean during study) Overall: 51.2 vs 48.7 (P = 0.619) Nocturnal: 4.78 vs 6.17 (P = 0.139) Severe: 0.10 vs 0.04 (P = 0.266)	+4.0 vs +4.5 (P = 0.224)
Robbins et al.[35]	R, OL, MC, MN, P/24 weeks (prior metformin and/or SU plus insulin)	LM50 (n = 158) vs glargine (n = 159) plus metformin (both arms)	Starting: 7.8% (both arms); ending 7.1% vs 7.5% (P < 0.001) Reduction from baseline to endpoint significantly greater for LM50 vs glargine (P < 0.001) Patients reaching target: ≤7%, 56.3% vs 39.7% (P = 0.005) ≤6.5%, 30.5% vs 14.4% (P = 0.001)	FBG: 8.1 vs 6.5 mmol/L (P < 0.001) PPBG: Breakfast 8.7 vs 9.2 mmol/L (P = 0.03) Lunch 8.4 vs 9.8 mmol/L (P < 0.001) Supper 8.7 vs 10.7 mmol/L (P < 0.001)	Episodes/patient per 30 days (mean at endpoint) Overall: 0.7 vs 0.3 (P = 0.02) Non-nocturnal: 0.5 vs 0.1 (P = 0.002) Nocturnal 0.2 each treatment Severe: 1.9% vs 1.3% of patients (NS)	+1.2 vs −0.5 (P < 0.001)

Table 1 Comparator trials including premixed insulin analog (Continued)

Reference	Study design/ duration	Study treatment (no. randomized patients)	HbA1c (mean)	Fasting and postprandial SMPG or SMBG†	Hypoglycemia	Weight gain + or loss − (mean, kg)
Malone et al.[37]	R, OL, MC, two-period CO/32 weeks (prior OADs)	LM25 vs glargine. Treatment arms (crossover design): LM25 then glargine (n = 52). Glargine then LM25 (n = 53) plus metformin (both arms)	Starting: 8.7%; ending: 7.4% vs 7.8% (P = 0.002). Reduction from baseline to endpoint significantly greater for LM25 vs glargine (P = 0.003). Patients reaching target: ≤7%, 42% vs 18% (P < 0.001)	FBG: 139.3 vs 123.9 mg/dL (P < 0.001). PPBG: Breakfast 156.4 vs 171.1 mg/dL (P = 0.012). Lunch NS§. Dinner 164.8 vs 193.8 mg/dL (P < 0.001)	Episodes/patient per 30 days (mean at endpoint). Overall: 0.68 vs 0.39 (P = 0.041). Nocturnal: 0.14 vs 0.24 (P = 0.788). No severe events	+2.3 vs +1.6 (P = 0.006)
Malone et al.[38]	R, OL, MC, two-period CO/32 weeks (prior insulin with or without OADs)	LM25 vs glargine. Treatment arms (crossover design): LM25 then glargine (n = 50). Glargine then LM25 (n = 47) plus metformin (both arms)	Starting 8.49%; ending: 7.54% vs 8.14% (P < 0.001). Reduction from baseline to endpoint significantly greater for LM25 vs glargine (P < 0.001). Patients reaching target: ≤7%, 30% vs 12% (P = 0.002)	FBG: 7.90 vs 7.39 mmol/L (P = 0.007). PPBG: Breakfast 9.44 vs 10.83 mmol/L (P < 0.001). Lunch (midday meal) 9.14 vs 10.65 mmol/L (P < 0.001). Dinner 9.59 vs 11.15 mmol/L (P < 0.001)	Episodes/patient per 30 days (mean at endpoint). Overall: 0.61 vs 0.44 (P = 0.477). Nocturnal: 0.14 vs 0.34 (P = 0.002). No severe events	+0.82 vs +0.06 (P = 0.001)
Jacober et al.[39]	R, MC, OL, two-period CO/32 weeks (prior OADs)	IMT‡ vs glargine. Treatment arms (crossover design): IMT then glargine (n = 31). Glargine then IMT (n = 29). Continuation of OADs (both arms)	Starting (prestudy): 9.21%; ending: 7.08% vs 7.34% (P = 0.003). Reduction from baseline (pretherapy¶ and prestudy) to end of therapy significantly greater for IMT vs glargine (P = 0.0068 and 0.0083, respectively). Patients reaching target: ≤7%, 44% vs 31% (P = 0.1026)	FBG:§ P > 0.05. PPBG: Breakfast 153.5 vs 172.1 mg/dL (P = 0.0034). Lunch 134.6 vs 157.9 mg/dL (P = 0.0001). Dinner 145.4 vs 161.9 mg/dL (P = 0.0066)	Episodes/patient per 30 days (mean at endpoint). Overall: 4.71 vs 2.31 (P = 0.0010). Nocturnal: 0.94 vs 0.93 (P = 0.9701). No severe events	+1.98 vs +1.52 (P = 0.457)
Kazda et al.[40]	R, OL, MC, P/24 weeks (prior OADs)	Insulin lispro (n = 52) vs LM50 (n = 54) vs glargine (n = 53)	Starting: 8.2% vs 8.1% vs 8.1%. Change from baseline to LOCF: −1.1% vs −1.2% vs −0.3% (lispro vs glargine, P = 0.001; LM50 vs glargine, P < 0.001). Patients reaching target: <7%, 40.4% vs 59.3% vs 24.5% (P-values NR)	FBG (change from baseline [9.8 vs 9.3 vs 9.6 mmol/L] to LOCF): −0.9 vs −0.9 vs −2.6 mmol/L (lispro vs glargine, LM50 vs glargine, P < 0.001). PPBG: Breakfast excursions (post- minus prebreakfast values; change from baseline [1.6 vs 2.7 vs 2.5 mmol/L] to LOCF):¶ −2.1 vs −1.8 vs −0.1 mmol/L (lispro vs glargine, LM50 vs glargine, P < 0.001). Breakfast (change from baseline [11.4 vs 11.9 vs 12.2 mmol/L] to LOCF): −3.0, −2.8, −2.6 mmol/L (lispro vs glargine, P < 0.01; LM50 vs glargine, P = 0.43). Lunch/dinner: mean values lower for lispro and LM50 vs glargine§ (P-values NR)	Episodes/100 patient-days (mean during treatment period): 1.4 vs 1.5 vs 1.0 (P-values NR). No severe events	+2.3 vs +1.8 vs +0.7 (P-values NR)

Table 1 Comparator trials including premixed insulin analog (Continued)

Reference	Study design/duration	Study treatment (no. randomized patients)	HbA1c (mean)	Fasting and postprandial SMPG or SMBG†	Hypoglycemia	Weight gain + or loss − (mean, kg)
Raskin et al.[41]	R, OL, MC, P/28 weeks (prior OADs)	BIAsp 30 (n = 117) vs glargine (n = 116) plus metformin and/or TZDs (both arms)	Starting: 9.7% vs 9.8%; ending: 6.91% vs 7.41% (P < 0.01). Reduction from baseline to end of study significantly greater for BIAsp 30 vs glargine (P < 0.01). Patients reaching target: <7%, 66% vs 40% (P < 0.001) ≤6.5%, 42% vs 28% (P < 0.05)	FPG: 127 vs 117 mg/dL (P > 0.05). PPPG (90 min PP)§: Breakfast (NS) Lunch (NS) Dinner (P < 0.05)	Minor (episodes/patient year) [mean, overall rate]: 3.4 vs 0.7 (P < 0.05). Major: 1 patient in glargine group	+5.4 vs +3.5 (P < 0.01)
Boehm et al.[42]	R, MN/24 months (prior OADs, biphasic insulin or short- and intermediate-acting insulin)	Initial 3 months: BIAsp 30 (n = 88) vs BHI 30 (n = 102) 21-month extension: BIAsp 30 (n = 58) vs BHI 30 (n = 67)‡‡	Starting: 8.11% vs 8.21% (start of 21-month extension); ending: 8.35% vs 8.13%. Baseline-adjusted treatment difference [BIAsp 30 minus BHI] after 24 months: 0.03% (P = 0.89). Patients reaching target: NR	NR	Major First year: 5% vs 8% of patients (P = 0.72) Second year: 0% vs 10% of patients (P = 0.04) Minor: Treatment-group difference in proportion of patients (NS)	+0.05 vs +2.0 (P = 0.07)
Niskanen et al.[43]	R, OL, MC, MN, two-period CO/24 weeks (prior insulin)††	BIAsp 30 vs LM25 (n = 137)	Starting: 8.5%; ending: 8.15% vs 8.01% (P = 0.082). BIAsp 30 was noninferior to LM25 (upper limit of 90% confidence interval for estimated difference [BIAsp 30 minus LM25] was <0.4%). Patients reaching target: NR	FBG (prebreakfast): 7.6 vs 7.5 mmol/L (P = 0.422). PPBG (90 min PP): Breakfast 9.5 vs 9.7 mmol/L (P = 0.524) Lunch 9.7 vs 9.8 mmol/L (P = 0.746) Dinner 9.6 vs 10.0 mmol/L (P = 0.186)	Major (during the two 12-week treatment periods): 1 patient in each group Minor and symptoms only (last 8 weeks of treatment): 0.69 vs 0.62 episodes/month (P = 0.292)	NR
Kilo et al.[46]	R, OL, P/12 weeks (prior metformin or metformin + SU or glinide)	BIAsp 30 (n = 46) vs NPH (n = 47) vs BHI 70/30 (n = 47) plus metformin (both arms)§§	Starting: 9.5% vs 9.5% vs 9.3%. Change from baseline to end of study: −1.3% vs −1.2% vs −1.1% (P-values NR). Patients reaching target: NR	FPG (change from baseline [241.8 vs 242.7 vs 227.2 mg/dL] to Week 12): −31% (−75 mg/dL) vs −37% (−91 mg/dL) vs −28% (−63 mg/dL) (P-values NR). PPPG§: −50 mg/dL reduction from baseline at each time point for each arm (NS)	Minor: 24% vs 13% vs 19% of patients (P-values NR) Nocturnal: 15% vs 23% vs 23% of patients (P-values NR) No major events	+0.7 vs +0.1 vs +1.0 (P = 0.251)

†Postprandial values recorded 2 h postprandial and based on mean daily glucose profiles at endpoint, unless specified otherwise.
‡LM50 before breakfast and lunch and LM25 before dinner.
§Actual values either not reported or only displayed graphically.
¶Primary endpoint.
††Glycemic control assessed after 12 weeks.
‡‡Efficacy and safety data presented for the subset of patients (n=125) with type 2 diabetes who entered the 21-month extension; the first 3 months included patients with type 1 and type 2 diabetes.
BIAsp 30, biphasic insulin aspart 70/30; BHI, biphasic human insulin; CO, crossover; DB, double-blind; FBG, fasting blood glucose; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; IMT, intensive mixture therapy including LM50 before breakfast and lunch, and LM25 before dinner; LM25, insulin lispro mix 25; LM50, insulin lispro mix 50; LOCF, last observation carried forward; MC, multicenter; MN, multinational; NPH, neutral protamine Hagedorn; NR, not reported; NS, not significant; OADs, oral antihyperglycemic drugs; OL, open-label; P, parallel; PP, postprandial; PPBG, postprandial blood glucose; PPPG, postprandial plasma glucose; R, randomized; SMBG, self-monitored blood glucose; SMPG, self-monitored plasma glucose; SU, sulfonylurea; TZD, thiazolidinediones.
§§Patient numbers represent those treated with the study regimens.

meals 4.4–5.6 mmol/L [80–100 mg/dL] and BG at bedtime 4.5–6.1 mmol/L [81–110 mg/dL]).

As treatment intensification, premixed insulin therapy after failure of a previous basal insulin only regimen is given in a dose amounting to half the total daily insulin dose given before breakfast and the other half given before dinner.[3] In a study by Rosenstock et al., the group treated with LM50 received one-third of the total daily insulin with each meal.[34] In a study by Robbins et al.,[35] patients who were previously treated with up to two insulin injections daily received introductory LM25 twice daily for 6 weeks and were randomized to one of two study groups; in the group treated with LM50, patients received 80% of the final dose of LM25 divided in three doses for each meal.

Patients with T2DM uncontrolled on oral BG-lowering agents can also receive premixed insulin BIAsp 30 either once (12 units at dinner), twice (adding 6 units at breakfast), or three times daily (adding 3 units at lunch) within 15 min of meal initiation. Dose titration consists of adding 2 units every 3 days to the chosen regimen. Dose regimens are chosen based on individual patient characteristics and treatment goals.[36]

Overview of the effects of premixed insulin over basal insulin: Efficacy and safety

Insulin lispro mixtures (LM25 and LM50)

In studies comparing twice-daily LM25 with once-daily insulin glargine,[19,37,38] a greater percentage of patients (insulin naïve or prior insulin and/or oral BG-lowering agents) achieved target HbA1c levels and better overall postprandial control with LM25 (see Table 1). Significantly higher hypoglycemia rates[19,37] and lower nocturnal hypoglycemia rates were reported in patients treated with LM25 versus glargine.[19,38] Weight gain was significantly higher with LM25 than glargine.[19,37,38]

The results from studies comparing thrice-daily premixed insulin analogues to once-daily insulin glargine demonstrated a greater change from baseline in HbA1c and a lower HbA1c at endpoint for the premixed insulins (see Table 1).[35,39,40] Robbins et al.[35] and Kazda et al.[40] reported significantly lower fasting BG levels at endpoint for glargine ($P < 0.001$) compared with LM50; however, Jacober et al.[39] found no difference between the intensive insulin mixture therapy approach (LM50 before breakfast and lunch and LM25 before dinner) and glargine in fasting BG. All three studies reported improved postprandial BG control with thrice-daily premixed insulin analogs compared with glargine.[35,39,40] More hypoglycemic events were seen in patients treated with thrice-daily premixed insulin analogues than in

patients treated with glargine,[35,39,40] but there were no differences between treatments in the occurrence of nocturnal hypoglycemia.[35,39]

Biphasic insulin aspart 70/30 (BIAsp 30)

Raskin et al. evaluated the efficacy and safety of BIAsp 30 twice daily versus insulin glargine once daily in insulin-naïve patients previously treated with oral BG-lowering agents (see Table 1).[41] More patients treated with BIAsp 30 achieved lower values of HbA1c ($P < 0.01$) and reached study target HbA1c values (<7%; $P < 0.001$) at endpoint than those treated with glargine. Hypoglycemia (minor), weight gain, and daily insulin doses were greater for patients treated with BIAsp 30 compared with glargine.

In a long-term efficacy and safety study of BIAsp 30 twice-daily versus biphasic human insulin (BHI) conducted by Boehm et al.,[42] there was no significant difference between treatments in HbA1c reduction or minor hypoglycemia events throughout the study. Major hypoglycemia events were significantly reduced during the second year of treatment in patients treated with BIAsp 30 (see Table 1).

A 12-week crossover study conducted by Niskanen et al.[43] demonstrated that treatment with BIAsp 30 was non-inferior to LM25 in terms of achieving target HbA1c levels. Hypoglycemic event profiles were similar in both groups (see Table 1).

Additional studies comparing postprandial BG control of BIAsp 30 and BHI once- or twice-daily dosing found that postprandial BG was significantly reduced by BIAsp 30 compared with BHI regardless of the injection time.[44,45]

Studies comparing other premixed insulin ratios

The PREFER study compared twice-daily BIAsp 30 with once-daily detemir plus insulin aspart with meals (intensive basal-bolus therapy).[31] Patients treated previously with basal insulin achieved a greater HbA1c reduction with detemir–insulin aspart than BIAsp 30; however, HbA1c reductions were similar in insulin-naïve patients treated with either regimen (see Table 1). Liebl et al.[31] concluded that patients already treated with basal insulin benefited more on a basal-bolus regimen, and that a premixed insulin regimen is an effective starter insulin in insulin-naïve patients. Increases in body weight were similar in both groups.

Kilo et al. evaluated the efficacy of simple starter once-daily insulin regimens (BIAsp 30, NPH, or BHI) plus metformin in patients with poorly controlled T2DM on oral BG-lowering agents.[46] All three regimens reduced

HbA1c values from baseline and lowered fasting BG (see Table 1).

Finally, Rosenstock et al. compared prandial LM50 therapy with basal-bolus (glargine–lispro) therapy in a 24-week study in patients with T2DM treated previously with insulin glargine plus oral BG-lowering agents.[34] Basal-bolus therapy led to a larger reduction in HbA1c, whereas both treatments resulted in body weight increases of 4.0 kg (LM50) and 4.5 kg (basal-bolus), similar to the weight changes observed in the 4-T study[21] (see Table 1).

Discussion

The progressive nature of T2DM translates into severe insulin deficiency; therefore, patients will eventually require insulin replacement. Results of trials such as INSTIGATE[18] and DURABLE[19,20] on populations of different ethnic origins support the initiation of insulin therapy at an early stage of the disease and even in newly diagnosed patients. In both these trials, patients with lower baseline HbA1c were able to meet and maintain glycemic targets for longer periods of time.

Of the three possible insulin starter regimens, premixed insulin analogs provide basal and prandial components in one single formulation that can be conveniently administered shortly before meals as often as once, twice, or three times daily. The efficacy and safety of premixed insulin analogs LM25, LM50, and BIAsp 30 have been compared with basal insulin regimens in insulin-naïve patients and after failure of oral BG-lowering therapy. Higher percentages of patients across these studies achieved target HbA1c (<7% or ≤7%), greater baseline to endpoint reductions in HbA1c, and better postprandial control with the premixed insulin analogues.[19,21,35,37-40] Despite the fact that there is convincing clinical evidence relating increased postprandial BG to disturbances in vascular function,[47,48] it has not yet been demonstrated that better postprandial control will lead to fewer complications. Even though more minor hypoglycemic events were seen with premixed insulin analogue treatment groups across the different studies, lower nocturnal hypoglycemia rates were observed with LM25.[19,38] Perhaps the minor hypoglycemic events can be controlled by implementing less aggressive titration schedules and by encouraging regular patient eating patterns. A meta-analyses[26] and systematic review[23] comparing basal, basal-bolus, and premixed insulins concluded that there were no differences among the three types of treatments in severe hypoglycemic events. More weight gain for premixed insulin has been reported across trials;[19–21,35–38,40,41] however, dietary management and exercise programs need to be put in place as part of the patient's treatment, especially when insulin is initiated.

Insulin premixes can be the appropriate choice for patients requiring both components of treatment (basal and bolus) but who have restrictions based on the complexity of the basal-bolus regimen. As with any T2DM therapy, insulin therapy in patients with T2DM should adapt to many factors, including age, comorbidities, risk of hypoglycemia, lifestyle, eating patterns, and psychological and socioeconomic context,[17] and should therefore be individualized.

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