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Clinical Experience with Insulin Glargine in Type 1 Diabetes

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Abstract

The Diabetes Control and Complications Trial (DCCT) demonstrated the importance of optimal glycemic control achieved through intensive insulin therapy in reducing the microvascular complications associated with type 1 diabetes. However, the DCCT, which was conducted prior to the availability of insulin analogs, also reported a significant increase in severe hypoglycemia with intensive versus conventional therapy. Insulin analogs were developed to aid patients in achieving better diabetes control by providing insulins with optimized pharmacokinetic and pharmacodynamic characteristics. Insulin glargine was the first long-acting insulin analog with a 24-h duration of action, offering once-daily injection, and has now been in clinical use for over 10 years. The authors performed a systematic search of EMBASE, MEDLINE, and Web of Science (Science Citation Index) to determine the efficacy of insulin glargine in type 1 diabetes in basal–bolus insulin regimens. Randomized controlled trials have demonstrated that glycemic control with insulin glargine is at least comparable to that with neutral protamine Hagedorn (NPH) insulin in adults and in children and adolescents, and with continuous subcutaneous insulin infusion in adults. However, these same trials show a significantly lower risk for hypoglycemia with insulin glargine compared with NPH insulin in adults.

Introduction

The Diabetes Control and Complications Trial (DCCT) demonstrated the importance of optimal glycemic control achieved through intensive insulin therapy in reducing the microvascular complications associated with type 1 diabetes.[1] However, the DCCT was conducted before the introduction of pharmacokinetically optimized insulin analogs with properties that offer patients an opportunity for greater control and flexibility in managing their blood glucose (BG) levels.[2] These properties are found in long-acting basal insulins, which have a longer duration of action, or in rapid-acting prandial insulins, which have a more rapid onset of action with reduced variability in activity.[2] Insulin glargine was the first basal insulin analog to be approved for patients with diabetes in the year 2000. This analog is modified in such a way that the insulin precipitates in the subcutaneous tissue following injection and is slowly absorbed into the bloodstream.[3]

The properties of the insulin analogs are designed to allow for more accurate replication of the basal and prandial components of insulin replacement with a reduced risk of hypoglycemia compared with equivalent human insulin.[2] Hypoglycemia is an important limiting factor in achieving glycemic control for patients with type 1 diabetes[4] and is a significant complication of intensive therapy. Indeed, in the DCCT, the rate of severe hypoglycemia was nearly threefold higher with intensive treatment compared with conventional therapy.[5] However, the clinical benefits of insulin analogs over regular human insulin (RHI) preparations remain controversial because meta-analyses have identified few advantages.[6–9] The aim of this review is to provide a descriptive summary of the overall clinical experience with insulin glargine versus neutral protamine Hagedorn (NPH) insulin or continuous subcutaneous insulin infusion (CSII) in adults or children and adolescents with type 1 diabetes as part of a multiple daily injection (MDI) regimen.

Search Strategy

Electronic databases (EMBASE, MEDLINE, and Web of Science [Science Citation Index]) were searched with a cutoff date of February 15, 2010 inclusive, using the key words "insulin," "glargine," and "type 1 diabetes."

The review was limited to randomized controlled trials in adult and in pediatric populations utilizing once-daily insulin glargine for a minimum of 12 weeks. Studies including pregnant women or other populations are not included in this review. Furthermore, reports that included patients with type 1 and type 2 diabetes were excluded if the authors did not provide separate data for the two diabetes groups.

Data Collection

The authors recorded the following information from each report (randomized controlled trials), where stated:

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- Study design
- Study duration
- Number of patients randomized
- Treatments allocated
- Change from baseline in glycosylated hemoglobin (A1C), fasting BG (FBG) or fasting plasma glucose, and 2-h postprandial BG (for rapid-acting insulins)
- Frequency of symptomatic and nocturnal hypoglycemia

Results and Discussion

The literature search retrieved 26 studies, in which insulin glargine was compared with NPH insulin (13 studies), ultralente (one study), or CSII (five studies) in adults (Table 1). Of these, four studies versus NPH and two studies versus CSII in adults were shorter than 12 weeks and were subsequently excluded. Six studies compared insulin glargine with NPH insulin/lente insulin in children and adolescents (Table 2); one of these studies was excluded because the duration of treatment was <12 weeks.

Clinical efficacy and safety with insulin glargine

Insulin glargine versus NPH insulin. The search identified nine randomized controlled trials that compared insulin glargine with NPH insulin as part of an MDI regimen, ranging in duration from 12 weeks[10] to 1 year[11] (Table 1). As summarized in this table, insulin glargine consistently provided significantly[10–13] or nonsignificantly[14] greater baseline-to-endpoint improvements in FBG than NPH insulin, and this was evident in studies ranging in duration from 12 weeks to 1 year. This difference was apparent both in studies where NPH was administered once daily and in studies where NPH was administered twice daily. The improvement in FBG with insulin glargine over NPH insulin was approximately 1–2 mmol/L. However, two studies reported improvements in FBG >3 mmol/L with insulin glargine.[15,16] The improvements in FBG were associated with small improvements in A1C with both insulins, although A1C increased slightly in one study.[14] In terms of the magnitude of A1C improvement, four studies showed no difference between the two insulins,[12,13,17,18] whereas four studies showed significantly greater improvements with insulin glargine compared with NPH insulin,[10,11,13,18] consistent with improvements in FBG. However, three of these studies used NPH insulin once daily,[10,11,16] and greater improvements in A1C may have been possible if NPH insulin was used twice daily or if there was an option to add a second daily dose of NPH insulin in these studies. For example, in the 30-week study by Fulcher et al.,[16] insulin glargine achieved greater improvements in A1C and FBG than once-daily NPH insulin. In contrast, in the study by Bolli et al.,[17] insulin glargine elicited significantly greater improvements in FBG than twice-daily NPH insulin, but the magnitude of A1C improvement was identical in both groups. Thus, it is possible that, although twice-daily NPH insulin does not seem to affect FBG, it may affect other parameters of glucose control, such as postprandial BG, to improve A1C.

Twice-daily insulin glargine has been tested in a crossover study in which 20 patients with type 1 diabetes were given once-daily insulin glargine at dinnertime or twice-daily insulin glargine (half doses at breakfast and dinner).[19] Over the 4-week treatment period, the twice-daily regimen resulted in lower BG levels after breakfast, lunch, and before dinner and was also associated with lower mean 24-h BG levels (7.1 vs. 8.8 mmol/L; $P = 0.031$) and less intraday variability in BG levels ($P = 0.044$). The authors concluded that for patients who experience late afternoon increases in BG levels, twice-daily insulin glargine may be a suitable alternative that does not require an increase in insulin dosage, although it is important to note that administering insulin glargine more than once daily is not currently approved by regulators and represents off-label use.

Another outcome that should be considered in the treatment of type 1 diabetes is the prevalence of hypoglycemia. Hypoglycemia is often debilitating and may lead to adverse outcomes. Therefore, in an effort to avoid hypoglycemia, patients may inadequately titrate their insulin, which may ultimately result in suboptimal glycemic control. Reviewing these nine studies, the authors found that insulin glargine was associated with a significantly reduced risk of symptomatic hypoglycemia[10,11,13,17,18] or no difference in risk[12,14–17] compared with NPH insulin. These differences were most marked in the studies that administered NPH insulin once daily. This difference in hypoglycemia between once-daily NPH and insulin glargine is reflected in the recommendations for a dose reduction of 20–30% when transitioning from once-daily NPH insulin to insulin glargine, while affording the same or better overall efficacy at lower doses.

Insulin glargine versus ultralente. The authors found only one study that compared insulin glargine with ultralente insulin. In this study, once-daily insulin glargine was shown to be associated with greater improvements in A1C and FBG and fewer episodes of hypoglycemia compared with once-daily ultralente.[20] However, this was a relatively small study, with only 22 patients, and should be interpreted with caution.

The "dawn phenomenon" and insulin glargine: implications on dose timing. The term "dawn phenomenon" describes hyperglycemia that occurs in the early morning.[21] Its causes are still not fully understood, but it seems to be related to a combination of the waning of the effects of intermediate-acting insulins, such as NPH insulin, before the next dose and to surges in circulating levels of other hormones, including growth hormone and cortisol, and a reduction in free insulin-like growth factor-1 (IGF-1) levels resulting in greater insulin resistance.[22–24] It has been suggested that as many as 54% of patients with type 1 diabetes experience the dawn phenomenon.[21] Patients with marked hyperglycemia are generally managed with CSII programmed to deliver an increased basal rate at an appropriate time during the night,[23] although there is some evidence to suggest that long-acting insulin analogs could also provide better control of early morning BG compared with NPH insulin. A nonrandomized study of 48 Japanese patients with type 1 diabetes treated with insulin glargine or NPH insulin as part of an MDI regimen, or CSII at a constant rate, evaluated nocturnal and early morning BG and free IGF-1 levels.[25] A total of 60% of patients receiving NPH insulin experienced the dawn phenomenon, whereas BG levels in the glargine and CSII groups were more stable, and few patients experienced the dawn phenomenon.[25] These differences corresponded with a marked reduction in free IGF-1 with NPH insulin, whereas IGF-1 levels remained relatively stable with CSII and insulin glargine. The authors concluded that the more constant insulin bioavailability with CSII or insulin glargine was effective in managing early-morning BG increases.

Table 1. Randomized Controlled Trials Comparing Insulin Glargine with NPH Insulin, Ultralente and Continuous Subcutaneous Insulin Infusion

Reference	Design	No. patients	Trial Duration	Treatments	Change from baseline		Frequency of hypoglycemia (episodes/patient–month, % patients)		Comment
					A1c (%)	FBG (mmol/L)	Symptomatic	Nocturnal	
vs NPH insulin									
Ratner 2000[13] (Study 3004)	Open-label, multicenter, parallel-group study	534	28 weeks	Bedtime glargine NPH (od or bd)	−0.16% (baseline 7.7%) −0.21% (baseline 7.7%) $P = 0.44$	−1.67 (FPG) −0.33 (FPG) $P = 0.0145$	39.9% 49.2% $P = 0.0219$	18.2% 27.1% $P = 0.016$	Lower FPG levels with fewer episodes of hypoglycemia with glargine compared with od- or bd NPH as part of a basal–bolus regimen
Raskin 2000[12]	Open-label, multicenter, parallel-group study	619	16 weeks	Glargine + lispro (od) NPH (od or bd) + lispro	−0.1% (baseline 7.6%) −0.1% (baseline 7.7%) $P = NS$	−30.6 −10.8 $P = 0.0001$	90.6% 90.6% $P = 0.84$	69.0% 63.1% $P = 0.06$	Glargine appears to be as safe and at least as effective as using NPH as basal–bolus treatment with lispro
Rossetti 2003[10]	Open-label, parallel-group study	51	12 weeks	Dinnertime glargine Bedtime glargine NPH (od) + lispro	−0.4% (baseline 7.0%) −0.4% (baseline 6.8%) +0.1% (baseline 6.9%) $P < 0.04$	7.6 ± 0.1[a] 7.6 ± 0.2[a] 8.1 ± 0.2[a] $P < 0.03$	8.1 ± 0.8[b] 7.7 ± 0.9[b] 12.2 ± 1.3[b] $P < 0.04$ vs NPH	1.7 ± 0.2 2.0 ± 0.19 3.6 ± 0.4 $P < 0.05$	Decreased A1c and hypoglycemia with glargine. In contrast to NPH, which should be given at bedtime, glargine can be administered at dinner time without deteriorating BG control
Porcellati 2004[11]	Open-label, parallel-group study	121	52 weeks	Dinnertime glargine + lispro NPH (od) + lispro	−0.4% (baseline 7.0%) 0.0% (baseline 7.0%) $P < 0.05$	7.6 ± 0.11[a] 8.1 ± 0.22[a] $P < 0.05$[a]	7.2 ± 0.5[b] 13.2 ± 0.6[b] $P < 0.05$[b]	0.3[c] 2.1c $P < 0.05$[c]	Glargine decreased A1c and reduced the frequency of hypoglycemia versus NPH
Hershon 2004[18] (Study 3004)	Subgroup analysis of Ratner study (2000)[6] of patients treated with NPH bd	394	28 weeks	Glargine (od) NPH (bd)	−0.09% −0.19% $P = NS$	−1.17 −0.56 $P = 0.015$	73.3%[d] 81.7%[d] $P = 0.02$	Severe 36.6%[e] Severe 46.2%[e] $P = 0.003$	Glargine was at least as effective as NPH in improving FBG control with fewer symptomatic hypoglycemic events
Home 2005[14] (Study 3001)	Open-label, multicenter, parallel study	585	28 weeks	Glargine + lispro NPH (od or bd) + RHI	+0.21 ± 0.05% (baseline 7.9%) +0.10 ± 0.05% (baseline 8.0%) $P = NS$	−1.17 −0.89 $P = 0.07$	89.0%[g] 84.6%[g] $P = NS$	61.0%[g] 61.1%[g] $P = NS$	Bedtime, glargine was as least as effective as NPH, without an increased risk of hypoglycemia

(continued)

Table 1. (Continued)

Reference	Design	No. patients	Trial Duration	Treatments	Change from baseline: A1c (%)	Change from baseline: FBG (mmol/L)	Frequency of hypoglycemia (episodes/patient–month, % patients): Symptomatic	Frequency of hypoglycemia (episodes/patient–month, % patients): Nocturnal	Comment
Fulcher 2005[16] (Study 4010)	Single-blinded, multicenter, parallel-group study	125	30 weeks	Glargine (od) + lispro	−1.04% (baseline 9.2%)	−3.46[h]	Severe 0.87[i]	Severe: 0.22[i]	Significantly lower A1c and FBG levels and less severe nocturnal hypoglycemia with glargine
				NPH (od) + lispro	−0.5% (baseline 9.7%)	−2.34[h]	Severe 0.99[i]	Severe: 0.37[i]	
					$P < 0.01$	$P = 0.032$	$P = NS$	$P = 0.02$	
Chatterjee 2007[15] (Study 6004)	Open-label, single-center, two-period crossover study using a BBT regimen	53	36 weeks	Glargine + aspart	−0.46% (baseline 8.53%)	−3.08	80.7%[j]	NR	Lower A1c and mean FPG (–54 mg/dL, $P = 0.002$), and greater satisfaction with glargine compared with NPH (DTSQ, $P = 0.001$)
				NPH (bd) + aspart	−0.26% (baseline 8.53%)	−0.08	77.2%[j]	NR	
					$P = 0.04$	$P < 0.01$	$P = 0.63$		
Bolli 2009[17] (Study 4019)	Parallel, open-label, multicenter study of patients switched from NPH	175	4-week run-in, 24 weeks treatment	Dinnertime glargine + lispro	−0.56% (baseline 7.82%)	−28.0 mg/dL	+0.26[k]	Serious (42 mg/dL) –0.19[k]	Lower FBG, lower BG variability and reduced nocturnal hypoglycemia with glargine. Similar changes in A1c, FBG, PPBG and incidence of hypoglycemia. Greater satisfaction and lower cost with glargine
				NPH (bd) + lispro	−0.56% (baseline 7.82%)	−9.8 mg/dL	+0.21[k]	−0.10 (<42 mg/dL)[k]	
					$P = NS$	$P = 0.0064$	$P = 0.953$	$P = 0.383$	

Reference	Design	No. pts	Trial duration	Treatments	A1c change from baseline (%)	24-h PG AUC (mmol/L/h)	PG AUC > 7.0 mmol/L (mmol/L/h)	PPPG AUC	Frequency of nocturnal hypoglycemia (episodes/patient-month)	Comments
Ashwell 2006[30] (Study 4006)	Open-label, multicenter, two-way crossover study	56	32 weeks (two 16-week periods)	Glargine +lispro	−0.5% (baseline 8.0%)	187	47	75	0.66 episodes	Glargine + lispro improved A1c and 24-h PG monitoring compared with NPH + RHI, with a reduction in nocturnal hypoglycemia
				NPH (od or bid) + RHI	0.0% (baseline 8.0%)	203	62	88	1.18 episodes	
					$P < 0.001$	$P = 0.037$	$P = 0.017$	$P = 0.002$	$P < 0.001$	

Reference	Design	No. patients	Trial Duration	Treatments	Change from baseline		Frequency of hypoglycemia (episodes/patient–month, % patients)		Comment
					A1c (%)	FBG (mmol/L)	Symptomatic	Nocturnal	
vs ultralente									
Kudva 2005[20]	Partially-blinded, multicenter, crossover study	22	16 weeks of treatment	Glargine (bedtime) + aspart	−0.12% (baseline 6.94%)	155 (at endpoint)	27.5 events	3	Lower A1c, nocturnal glycemic variability and hypoglycemia with glargine
				Ultralente (bedtime) + aspart	+0.08%	191 (at endpoint)	31.5 events	2	
					$P = 0.03$	$P = 0.047$	$P = 0.0455$	$P = NS$	
vs CSII									
Lepore 2003[32]	Open, parallel-group study in patients previously on NPH	32	52 weeks	CSII with lispro + boluses at meals ($n = 16$)	−1.0% (baseline 9.2%), $P < 0.001$	−3.8% (baseline 11.9), $P < 0.001$	Severe: 0.12 vs 0.37 on NPH, $P < 0.05$	NR	Both CSII and MDI with lispro + glargine improved metabolic control and reduced severe hypoglycemia in patients not controlled on NPH as baslin insulin
				Lispro + dinner or bedtime glargine ($n = 16$)	−0.6% (baseline 8.5%), $P < 0.001$	−1.8 (baseline 12.3), $P < 0.001$	Severe: 0.18 vs 0.43 episodes per patient/year, $P < 0.05$	NR	
					$P = NS$	$P = NS$	$P = NS$		
Bruttomesso 2008[36]	Multicenter, open-label, randomized. crossover study	39	6 months	CSII with lispro ($n = 24$)	−0.2% (baseline 7.3%)	BG variability 5–12% vs MDI[L]	Moderate: 1.1 ± 1.7 episodes per patient	Severe: 0.1 ± 0.3	Glucose variability was lower with CSII, with better glycemic control and higher treatment satisfaction than with glargine
				MDI with glargine + lispro ($n = 15$)	−0.17% (baseline 7.3%)	NR	1.3 episodes per patient	0.1 ± 0.4	
					$P = NS$	$P < 0.05$	$P = 0.327$	$P = 0.710$	
Bolli 2009[37] (Study 4036)	Randomized, open, multicenter study of people previously on NPH	50	24 weeks	CSII (lispro)	−0.7 ± 0.7% (baseline 7.7%)	−3.3 (baseline 10.1)	1152 events by 23 of 28 patients (82%)	3 events per patient	In people naïve to CSII or glargine, glycemic control is similar with glargine vs the more expensive CSII therapy
				Glargine + lispro	−0.6 ± 0.8% (baseline 7.8%)	−2.7 (baseline 10.4)	1022 events by 27 of 29 patients (93%)	5 events per patient	
					$P = NS$	$P = NS$	$P = NS$	$P = 0.34$	

[a]Mean daily blood glucose; [b]Mild hypoglycemia (self-assisted episodes, blood glucose ≤ 4.0 mmol/L) episodes/patient-month; [c]Episodes occurred at an earlier time at night (01:00–04:59); [d]Percentage of patients with at least one symptomatic event confirmed by BG of < 2.8 mmol/L; [e]Percentage of patients with at least one symptomatic event confirmed by BG of < 2.0 mmol/L; [f]Mean total number of episodes per patient; [g]Percentage of patients with at least one episode; [h]Adjusted least-squares mean change from baseline. Unadjusted A1c change was −0.89% in glargine group and −0.67% in NPH group ($P < 0.05$); [i]Events per 100 patient-days; [j]Mean incidence of both severe and non-severe hypoglycemia; [k]Mean change in overall events (diurnal and nocturnal) episodes/patient/month; FBG = fasting blood glucose; NPH = neutral protamine Hagedorn insulin; od = once daily; bd = twice daily; NS = not significant; FPG = fasting blood glucose; RHI = regular human insulin; NR = not reported; BBT = basal–bolus therapy; DTSQ-diabetes treatment satisfaction questionnaire; BG = blood glucose; PPBG = postprandial blood glucose; CSII = continuous subcutaneous insulin infusion; MDI = multiple daily injections; PG = plasma glucose; AUC = area under curve; CGMS = continuous glucose monitoring system; glargine = insulin glargine.

Table 2. Randomized Controlled Trials in Children/Adolescents Comparing Insulin Glargine with NPH Insulin, Ultralente and Continuous Subcutaneous Insulin Infusion

					Change from baseline		*Frequency of hypoglycaemia (episodes/pt-month, % patients)*		
Reference	*Design*	*No. Pts*	*Trial Duration*	*Treatments*	*A1C (%)*	*FBG (mmol/L)*	*Symptomatic*	*Nocturnal*	*Comments*
Schober 2002[66] (Study 3001)	Multicenter, open-label, parallel group in children/ adolescents aged 5–16 years	349	24 weeks	Bedtime Glargine	+0.28% (baseline NR)	−1.29 mmol/L	Severe: 23%	Severe 13%	Once-daily glargine provides effective glycaemic control and is well tolerated in children and adolescents.
				NPH (od or bd)	+0.27% (baseline NR)	−0.68 mmol/L	Severe: 29%	Severe: 18%	
					$P = 0.93$	$P = 0.02$	$P = 0.22$	$P = 0.19$	
Murphy 2003[64]	Open-label, cross-over study	28	32 weeks	Glargine (pre-bedtime) + lispro	−0.6% (baseline 9.3%)	FBG 8.0 2-h post breakfast 8.1	NR	32% nights	Glargine + lispro reduced nocturnal hypoglycemia and was at least as effective as NPH + RHI in maintaining glycemic control in adolescents on multiple injection regimens.
				NPH (pre-bedtime) + RHI	−0.2% (baseline 9.3%)	FBG 9.0, 2-h post breakfast 10.7	NR	56% nights	
					$P = 0.13$	Both $P < 0.0005$	NR	$P < 0.05$	
Mianowska 2007[68]	Prospective cross-over study in children aged 6–12 years	14	6 months	Glargine	At 4 months: −0.6% (baseline 7.7%)	−1.8 (baseline 9.8)	NR	No severe hypoglycaemia	Glargine provides better early morning and good glycaemic control, no increase in risk of severe hypoglycaemia.
				NPH	At 4 months: 0.0% (baseline 7.7%)	−0.5 (baseline 9.8)	NR	NR	
					$P = 0.007$	$P = 0.077$			
Chase 2008[62] (Study 4030)	Open-label, multicenter parallel group	175	4 week run in period, 24 weeks	Glargine (od) + lispro ($n = 85$)	−0.25% ± 0.14% (baseline 7.8%)	Fasting SMBG: −3.3 mg/dL	Severe: 0.20 events per patient year	Confirmed BG <70 mg/dL[b]116 events per patient per year	Glargine is well tolerated for pediatric patients and may be more efficacious than NPH/lente in those with elevated A1C
				NPH/lente (bd) ($n = 90$)	−0.05% ± 0.13% (baseline 8.0%)	Fasting SMBG: +1.1 mg/dL	Severe: 0.09 events per patient year	94 events per patient per year	
					$P = 0.1725$[a]	$P = 0.6962$	$P = 0.1814$	$P = 0.0298$	
Hassan 2008[67]	Single center, parallel group study	42	3 months	Glargine (bd) + rapid acting insulin mixed in same syringe	−0.1% (baseline 6.8%)	6.0	0 events	NR	Glycemic control with glargine mixed with rapid-acting insulin analog bd was better than standard NPH therapy in newly diagnosed T1DM.
				NPH (bd) + rapid acting insulin	+0.7% (baseline 6.9%)	10.3	7 events	NR	
					$P < 0.029$	$P < 0.008$			

[a]Analysis of covariance, adjusting for baseline A1C, revealed a strong study arm effect on the slopes of the regression lines, indicating that the reduction in HbA1c was significantly greater with insulin glargine in those patients with higher baseline A1C values; [b]no differences in the occurrence of glucose levels <50 mg/dL ($P = 0.82$) or <36 mg/dL ($P = 0.32$) were found between the 2 groups. FBG = fasting blood glucose; NS = not significant; NR = not reported; FAA = fast-acting analogue; RHI = regular human insulin; BG = blood glucose; SMBG = self-monitored blood glucose; od = once-daily; bd = twice-daily; NR = not reported; NPH = neutral protamine Hagedorn insulin; glargine = insulin glargine.

Pharmacokinetic and pharmacodynamic studies have revealed that insulin glargine has a longer duration of action than NPH insulin. However, the duration of action of insulin glargine may not reach 24 h in some people,[26,27] which may be reflected by hyperglycemia shortly before the next administration. In one clinical study that compared the effects of timing of insulin glargine administration (lunchtime, dinnertime, and bedtime) (Table 3), plasma insulin levels tended to wane shortly before the injection, corresponding to a small increase in plasma glucose levels.[28] This effect was most notable for the dinnertime injection. In a similar study, the FBG levels did not change during the 24-week treatment period when insulin glargine was injected at breakfast, similar to the dawn phenomenon.[29] The results of these studies suggest that changing the time of insulin glargine injection to lunchtime or bedtime should avoid hyperglycemia before the next insulin glargine injection. This may be explained by the shorter intervals between breakfast and lunch and between dinner and bedtime, compared with that between lunch and dinner, thus providing sufficient insulin cover from the prandial insulin to overcome any waning of insulin glargine.[28]

Combining insulin glargine with a rapid-acting insulin

As outlined in the previous section, the use of insulin glargine versus other long- and intermediate-acting insulins as part of an MDI regimen in type 1 diabetes has been extensively studied. Almost all of the studies of insulin glargine to date either used insulin glargine in both groups and compared the efficacy of short-acting insulins at mealtimes or used the same short-acting insulin in both groups to compare the efficacy of basal insulin (as described above). The results of studies that compared short-acting insulins alone are beyond the scope of the present review. To the authors' knowledge, only one study in type 1 diabetes has compared insulin glargine plus a rapid-acting analog (insulin lispro) versus NPH insulin in combination with RHI.[30] In that 32-week, two-way crossover study (16 weeks per treatment period), insulin glargine plus insulin lispro achieved a significantly lower A1C compared with NPH insulin plus RHI (7.5% vs. 8.0%; $P < 0.001$). This was associated with significantly lower 24-h glucose area under the curve (AUC) (187 vs. 203 mmol/L/h; $P = 0.037$), plasma glucose AUC >7 mmol/L (47 vs. 62 mmol/L/h; $P = 0.017$), and postprandial plasma glucose AUC (75 vs. 88 mmol/L/h), although not nighttime plasma glucose AUC or plasma glucose AUC <3.5 mmol/L. The total rate of symptomatic hypoglycemia was comparable (1,277 vs. 1,327 episodes), but the rate of symptomatic nocturnal hypoglycemia was significantly lower with insulin glargine plus insulin lispro (0.66 ± 0.02 vs. 1.18 ± 0.02 episodes/month; $P < 0.001$). Most episodes of nocturnal hypoglycemia occurred at 06:00–0:700 h with insulin glargine plus insulin lispro versus 00:00–04:00 h with NPH insulin plus RHI.

Insulin glargine-based MDI therapy versus CSII

The authors found three clinical studies that compared insulin glargine-based MDI with CSII, all of which used insulin lispro in the CSII group.[31–37] As summarized in Table 1, these studies show comparable or marginally greater improvements in glycemic control and lower rates of hypoglycemia with CSII versus MDI therapy with insulin glargine, indicating that CSII may be more effective than MDI therapy with insulin glargine. However, most of these studies were relatively small in size, limiting the ability to detect differences in either regimen. In addition, CSII allows the delivery of multiple basal rates, which might help mitigate the dawn phenomenon. Larger, better-designed studies with appropriate powering may help to better understand the relative impact of CSII and insulin glargine-based MDI on glycemic control and hypoglycemia in patients with type 1 diabetes.

Implications of insulin analogs for the treatment of type 1 diabetes in adults

As described above, insulin analogs provide improved pharmacokinetic and pharmacodynamic characteristics relative to the respective human insulin. Since their introduction, it has been proposed that these properties confer advantages for the treatment of diabetes, particularly in terms of reduced risk of hypoglycemia, which has been demonstrated in meta regression analyses for insulin glargine[6] and insulin detemir.[9] The reduced risk of hypoglycemia with insulin glargine relative to NPH insulin may enable more patients to achieve treatment targets, through more aggressive titration of the insulin dose. Studies show that basal insulin analogs provide potentially important improvements in glycemic control that should reduce the risk of diabetes-related complications with long-term intensive therapy. The flexibility of insulin glargine dosing in relation to timing of administration has also been demonstrated (and approved by the Food and Drug Administration)—in particular, the opportunity for administration at breakfast, dinnertime, or bedtime, providing the timing of daily injection is constant.[28,29,38]

As described previously in this review, insulin analogs provide clinically important improvements in glycemic control within a tightly controlled clinical trial setting; but how is this evidence reflected in everyday clinical practice? Observational studies are generally regarded as the best approach to assess the actual health outcomes of patients in routine care.[39,40] This is because the level of care patients receive in clinical trials is often of a different standard and not representative of that seen in daily clinical practice, particularly with respect to patient populations and medication adherence.[41,42] In addition, clinical trials may include a limited scope of titration with other glucose-lowering drugs (or other concomitant treatments), a relatively short observational period, and potential for population bias, which may prevent extrapolation of findings to everyday practice.[43,44]

Therefore, what is the evidence in less rigorously controlled settings, where patients may receive less support from their clinician? There is ample evidence from everyday clinical practice to demonstrate the efficacy of insulin analogs.[45–61] Switching to insulin analog-based MDI regimens was associated with marked improvements in glycemic control. For example, in an observational study of 1,942 patients who were switched from NPH insulin to insulin glargine, mean A1C declined by 0.8% over 6 weeks of treatment, from 8.0% at baseline.[56] In a second study of longer duration, 1,447 patients who were switched from various insulin regimens to basal–bolus therapy with insulin glargine and insulin glulisine experienced a significant mean reduction in A1C of 1% over 6 months from a baseline of 8.0%.[54] These findings support the evidence gained in randomized controlled trials. Nevertheless, one must interpret such studies with care, because of the lack of a comparator group, and the potential for bias through patient

Table 3. Studies Evaluating Timing of Insulin Glargine Administration

Reference	Design	No. patients	Trial duration	Treatments	Change from baseline		Frequency of hypoglycemia (episodes/patient–month, % patients)		Comments
					A1c %	FBG (mmol/L)	Symptomatic	Nocturnal	
Hamann 2003[29] (Study 4007)	Open-label, multicenter, parallel-group trial	378	24 weeks treatment	Breakfast glargine + lispro	−0.2% (baseline 7.6%)	+0.1 ± 2.6	92.6%	59.5%, $P = 0.29$ vs bedtime and dinner time	No clinically relevant difference in efficacy when glargine administered before breakfast, before dinner, or at bedtime
				Dinnertime glargine + lispro	−0.1 % (baseline 7.5%)	−1.2 ± 2.7	93.8%	71.9%, $P = 0.0013$ vs breakfast	
				Bedtime glargine + lispro	−0.1% (baseline 7.6%)	−1.3 ± 2.5	96.9%	77.5%	
					P = NS	P = NS	P = NS		
Ashwell 2006[28]	Three-way cross over study to determine the optimal timing of injection of once-daily glargine in people using lispro at mealtimes	23	16 weeks	Lunchtime glargine + lispro	Endpoint: 9.2 ± 0.3%	8.6 ± 0.7	9.4 ± 0.9	9.1 ± 0.6	BG levels rise around the time of glargine administration, whatever the time. Bedtime dosing leads to hyperglycemia in the early part of the night which is improved by giving insulin glargine at lunch time or dinner time
				Dinnertime glargine + lispro	Endpoint: 8.2 ± 0.3%	6.4 ± 0.7	4.9 ± 0.9	7.8 ± 0.6	
				Bedtime glargine + lispro	Endpoint: 8.0 ± 0.3%	6.4 ± 0.8	7.4 ± 1.1	6.7 ± 0.6	
					$P = 0.016$	$P = 0.051$	$P = 0.007$	$P = 0.023$	
Grimaldi 2007[38] (Study 4024)	Open-label, multicenter, parallel-group, non-inferiority study	1178	26 weeks	Dinnertime glargine (18:30–21:00) + FAA (75%) or RHI (25%)	−0.25 ± 0.66% (baseline 8.01%)	NR	Severe: 6.85%	NR	No difference in A1C variation, FBG decrease, severe hypoglycemia or weight change: equivalence between regimens shown
				Bedtime glargine (22:00 – 24:00) + FAA or RHI	−0.24 ± 0.76% (baseline 8.08%)	NR	Severe: 5.69%	NR	
					P = NS	P = NS	P = NS		

FBG = fasting blood glucose; NS = not significant; NR = not reported; FAA = fast-acting analogue; RHI = regular human insulin; BG = blood glucose; SMBG = self-monitored blood glucose; od = once-daily; bd = twice-daily; NPH = neutral protamine Hagedorn insulin; glargine = insulin glargine.

selection, and limited data collection—hypoglycemia, for example, is often under-reported in such studies.

Insulin analogs in children and adolescents

Several studies have been performed to evaluate the efficacy of insulin glargine in children and adolescents. These studies are important because type 1 diabetes is usually diagnosed at a young age, and pediatric treatment represents an important aspect of managing the condition. The literature search identified six studies (seven publications)[62–68] in children, ranging in duration from 9 weeks to 32 weeks (Table 2). However, the small sample size (<50 patients) in most of these studies limits their validity. The other two studies enrolled 349 and 175 patients and compared insulin glargine with either NPH insulin (once or twice daily)[65,66] or NPH insulin/lente insulin.[62] In the study by Schober et al.[65,66] with children and adolescents 5–16 years of age, insulin glargine was associated with significantly greater improvements in FBG, although this did not translate into improvements in A1C. In the study by Chase et al.[62] in adolescents and teenagers 9–17 years of age, there were no differences in the magnitude of improvement in A1C. However, after adjusting for baseline A1C, the change in A1C was significantly greater with insulin glargine than with NPH insulin/lente insulin. In terms of hypoglycemia, the study by Schober et al.[65,66] revealed no difference in the rate of hypoglycemia, whereas the study by Chase et al.[62] revealed higher rates of confirmed hypoglycemia with BG <70 mg/dL (116 vs. 94 events/patient-year, $P = 0.0298$).

Treatment flexibility and treatment satisfaction

Insulin analogs provide several functional advantages that may increase treatment satisfaction for patients with diabetes. Clinical studies show that insulin glargine provides flexible basal insulin control with the option of once-daily administration at any time of day.[28,29,38] Insulin glargine, compared with NPH insulin, is also associated with lower rates of hypoglycemia, a side effect that patients find particularly distressing. Rapid-acting insulin analogs provide flexibility, with the possibility of injecting immediately after a meal constituting an important advantage because of the potential to administer a dose of insulin appropriate for the meal size/content. It has been reported that insulin analogs are associated with greater treatment satisfaction relative to NPH insulin in patients with type 1 diabetes.[69,70] Ashwell et al.[69] compared quality of life (QoL) and treatment satisfaction with MDI regimens based on insulin glargine plus insulin lispro versus NPH insulin plus RHI. Over 32 weeks of treatment, insulin glargine plus insulin lispro significantly improved treatment satisfaction and patient QoL compared with the NPH plus RHI regimen.

However, data on the impact of insulin therapy on patient satisfaction and QoL remain limited in type 1 diabetes. These outcomes should be evaluated in more detail in future clinical trials because there is some evidence that such factors not only influence patients' perceptions of their condition, but also their adherence to treatment. Indeed, patients reporting poor QoL or poor treatment satisfaction may be less likely to adhere to their treatment.[71–73] Furthermore, as reported by Samann et al.,[74] flexible, intensive insulin therapy with dietary freedom can achieve significant improvements in glycemic control without increasing the risk of severe hypoglycemia. Such treatment flexibility with insulin analogs[75] may be especially important to reduce the incidence of hypoglycemia in children and adolescents, particularly considering their unpredictable lifestyles.

Limitations

The authors performed a comprehensive literature search to retrieve reports describing the use of insulin glargine versus NPH insulin for the treatment of type 1 diabetes. However, some limitations should be discussed. First, the search was limited to EMBASE, MEDLINE, and Web of Science. However, it is possible that some studies published in journals not indexed in any of these databases were missed, particularly non-English journal articles. Second, the present analysis was limited to randomized controlled trials; this is recommended to avoid possible bias associated with non-randomized cohort studies or retrospective reviews of medical databases. However, the authors identified a large number of such studies involving several thousand patients that may greatly influence the overall interpretation, as such studies may better reflect everyday clinical practice and patient expectations for treatment. Third, although QoL is an important factor in the holistic effects of insulin therapy, few studies to date have assessed QoL or reported data if the studies did assess QoL. Moreover, the reports that did include QoL did not routinely use the same questionnaire(s). Therefore, a meaningful assessment of QoL could not be provided by this review.

Conclusions

This review provides a summary of the considerable evidence obtained for insulin glargine in type 1 diabetes since its approval, representing more than 10 years of clinical experience. The data show that insulin glargine provides consistent insulin delivery lasting up to 24 h, which permits once-daily dosing. Insulin glargine provides glycemic control that is at least comparable with NPH insulin, particularly once-daily NPH insulin, in adults, adolescents, and children. However, insulin glargine is also generally associated with a significantly lower risk of hypoglycemia compared with NPH insulin in adults. This latter observation represents an important clinical difference given the fact that hypoglycemia is established as one of the key limiting factors in the achievement of glycemic control. There is also some evidence to suggest that, as part of an MDI regimen, combining insulin glargine with a rapid-acting insulin analog provides benefits over intermediate- and short-acting human insulin-based regimens. The literature search revealed no evidence to demonstrate the superiority of insulin glargine-based MDI or CSII. However, the paucity of well-designed, large-scale trials means more studies are needed in this area.

In conclusion, basal–bolus insulin regimens or CSII should be considered a treatment of choice for type 1 diabetes. The use of long- and short-acting insulin analogs within these regimens offers significant clinical advantages over intermediate- and short-acting human insulins that may enable more patients to reach glycemic targets and reduce the considerable burden of complications associated with poor control in patients with type 1 diabetes.

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