Journal of Diabetes and Its Complications 33 (2019) 236–242

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Efficacy and safety of insulin glargine/lixisenatide (iGlarLixi) fixed-ratio combination in older adults with type 2 diabetes

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ARTICLE INFO

Article history:
Received 22 June 2018
Received in revised form 2 November 2018
Accepted 23 November 2018
Available online 30 November 2018

Keywords:
Type 2 diabetes
Elderly
Fixed-ratio combination
iGlarLixi
Lixisenatide
Insulin glargine

ABSTRACT

Aims: This study assessed the efficacy and safety of iGlarLixi (a titratable, fixed-ratio combination of insulin glargine [iGlar] plus lixisenatide) in older patients with type 2 diabetes.
Methods: This post hoc analysis used patient-level data from patients aged ≥65 years from the phase III LixiLan-O and LixiLan-L studies, which compared iGlarLixi with iGlar and lixisenatide (LixiLan-O only). Efficacy endpoints were changes in glycated hemoglobin A1C, fasting plasma glucose, postprandial glucose, weight, and achievement of A1C <7.0% (53 mmol/mol). Safety measures included incidence of documented symptomatic hypoglycemia (defined as typical symptoms of hypoglycemia plus self-measured plasma glucose ≤70 mg/dL [3.9 mmol/L]), severe hypoglycemia (requiring assistance of another person), and incidence of gastrointestinal adverse events. Results were compared with those from patients aged <65 years.
Results: In both trials, older patients treated with iGlarLixi achieved significantly greater reductions in A1C at Week 30 than comparators. Treatment with iGlarLixi mitigated insulin-associated weight gain and lixisenatide-associated gastrointestinal events. Results were largely comparable between patients aged ≥65 versus <65 years.
Conclusions: iGlarLixi provides significant improvements in glycemic control in patients aged ≥65 years without increasing hypoglycemia risk. As a once-daily injection, it simplifies treatment regimens and may contribute to improved adherence in this patient population.

Declaration of interest: Y.H. received research support from, was a member of the speaker's bureau, and was an author for Aegerion, Amarin Pharma Inc., Amgen Inc., AstraZeneca, Boehringer Ingelheim, Boehringer Ingelheim-Lilly, Bristol-Myers Squibb, Gan & Lee, Gilead, Grifols, Hanmi, Intarcia, Janssen, Lexicon Pharmaceuticals Inc., Lilly, Merck, Merck-Pfizer, Mylan, Novo Nordisk, Regeneron, and Sanofi.

C.C. has no conflict of interest.

T.D. is an employee and stock/shareholder of and author for Sanofi US.

F.G. was a consultant and author for AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Merck Sharp and Dohme, Roche Diabetes Care, and Takeda. He received research support from and was an author and consultant for Eli Lilly, Lifescan, Sanofi, and Takeda.

N.S. was a member of the advisory panel of and author for AstraZeneca, Boehringer Ingelheim, Intarsia, Janssen Pharmaceuticals, Lilly, Novartis, Sanofi US, and Teva. He was also a member of the advisory panel and speaker's bureau of and author for AstraZeneca and Boehringer Ingelheim. He received research support from AstraZeneca, Boehringer Ingelheim, and Sanofi.

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J.F. was a consultant and on advisory boards for AstraZeneca, BMS, Echosens, Elcelyx, Johnson and Johnson, Ligand, Novo Nordisk, Sanofi. He received research support from AbbVie, Allergan, AstraZeneca, Boehringer Ingelheim, BMS, Elcelyx, Eli Lilly, Genentech, IONIS, Janssen, Johnson and Johnson, Lexicon, Ligand, Madrigal, Merck, Mylan, Myovant, Novartis, Novo Nordisk, Ogeda, Pfizer, Sanofi, TaiwanJ, and Theracos.

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https://doi.org/10.1016/j.jdiacomp.2018.11.009

1. Introduction

The Centers for Disease Control and Prevention estimate that 20.8% of older adults (aged ≥65 years) in the US have diagnosed diabetes.[1] The medical, societal, and personal burdens of type 2 diabetes in this population are substantial, and these patients are at increased risk of acute and chronic microvascular and cardiovascular complications, excess mortality, reduced functional status, and institutionalization.[2] Management of diabetes in older patients may be complicated by their clinical, cognitive, and functional status, along with issues related to polypharmacy,[3] making it particularly important to simplify treatment regimens in this patient population.

The American Diabetes Association (ADA) guidelines recommend assigning less-stringent glycemic goals for older patients, using individualized criteria and a target glycated hemoglobin A1C (A1C) of <8.0–8.5% (64–69 mmol/mol) for patients with multiple coexisting chronic illnesses.[4] In the US (for the years 2007–2010), 84.2% of adults aged ≥65 years met an A1C target of <8.0% (64 mmol/mol), with 84.9% of those aged ≥75 years also meeting this target.[5] These statistics suggest that a significant number of older patients could still benefit from improved diabetes care, with individualized goals being set to lessen the risk of hypoglycemia and other adverse events (AEs).[6] The concept of patient-centered management and individualized treatment goals is also supported by guidelines from the American Geriatric Society, along with the ADA and the American Association of Clinical Endocrinologists.[4,6,7]

Despite the high prevalence of diabetes in older adults, they are often excluded or underrepresented in clinical trials for treatment of type 2 diabetes — either due to age, inclusion criteria, or because of the presence of one or more confounding comorbidities.[2] Therefore, decisions regarding hypoglycemia risk, treatment complexity, and weight gain associated with treatment (all of which are factors integral to individualizing patient care) are often made using evidence extrapolated from younger patients. Reducing the risk of hypoglycemia is particularly important for older patients who may be at greater risk of hypoglycemia unawareness or hypoglycemia-associated complications such as falls, related fractures, or acute cardiovascular events.[3] Yet, there is generally limited evidence upon which to base clinical decisions regarding optimal therapy in older patients.

iGlarLixi combines basal insulin glargine (iGlar) 100 units/mL and lixisenatide in a titratable, fixed-ratio combination that is administered as a single, daily injection. The rationale for the combination of basal insulin (BI) with a short-acting glucagon-like peptide 1 receptor agonist (GLP-1 RA) for the management of type 2 diabetes is based on the complementary mechanisms of action of the agents. iGlar predominantly improves fasting plasma glucose (FPG) by inhibiting hepatic glucose production and increasing peripheral glucose uptake,[8] whereas lixisenatide improves postprandial glucose (PPG) by enhancing glucose-stimulated insulin secretion, reducing glucagon secretion, and delaying the rate of gastric emptying.[9] The addition of lixisenatide to iGlar was shown to improve A1C, fasting hyperglycemia, and postprandial hyperglycemia while mitigating weight gain in the phase III GetGoal clinical trials.[10,11] Co-formulating both agents in a titratable fixed-ratio combination for once-daily injection may help ameliorate the potential problems of adherence to treatment with multiple agent combinations, thereby resulting in patients taking medications for longer periods of time.[12,13]

We performed a post hoc analysis of data from older adults (aged ≥65 years) who participated in two large, phase III clinical trials that investigated iGlarLixi in the treatment of insulin-experienced (LixiLan-L trial; NCT02058160) and insulin-naive (LixiLan-O trial; NCT02058147) patients with type 2 diabetes. These trials demonstrated that iGlarLixi-treated patients were more likely to achieve glycemic targets vs. comparators. Both trials showed a beneficial effect of iGlarLixi on body weight, no additional risk of hypoglycemia compared with iGlar, and lower levels of gastrointestinal side effects when compared with lixisenatide alone.[14,15] Since these studies did not have an upper age limit for patient inclusion, a significant proportion of older patients were assessed in these trials (31.3% and 26.1% of patients were aged ≥65 years in the LixiLan-L and LixiLan-O trials, respectively). This manuscript focuses on the efficacy and safety of iGlarLixi in patients aged ≥65 years.

2. Research design and methods

2.1. Study design

LixiLan-L and LixiLan-O were phase III, randomized, open-label, parallel-group studies investigating the efficacy and safety of iGlarLixi in patients with type 2 diabetes. The full details of the trials have been presented elsewhere and are summarized here.[14,15]

The LixiLan-L trial enrolled patients with type 2 diabetes inadequately controlled on BI for at least 6 months (with a stable insulin regimen for at least 3 months) and with stable doses of BI (15–40 units/day ± 20%) for at least 2 months with or without oral antidiabetic drugs (OADs). Any OAD other than metformin was discontinued at the start of the 6-week run-in phase; patients not already using iGlar were switched to iGlar, and the daily dose was optimized to achieve mean fasting self-measured plasma glucose (SMPG) of <140 mg/dL (7.8 mmol/L) for all patients. Eligible patients were randomized in a 1:1 ratio to receive once-daily open-label treatment with iGlarLixi or iGlar for 30 weeks. The LixiLan-O trial enrolled patients with type 2 diabetes inadequately controlled on metformin with or without a second OAD. Any OAD other than metformin was discontinued at the start of the 4-week run-in phase, during which the daily dose of metformin was optimized to 2000 mg or a maximally tolerated dose. Eligible patients were randomized in a 2:2:1 ratio to iGlarLixi, iGlar, or lixisenatide, respectively, added to ongoing metformin therapy for 30 weeks. After randomization, and in both trials, iGlarLixi and iGlar were titrated to target mean fasting SMPG of <100 mg/dL (5.6 mmol/L); the maximum allowed dose for iGlarLixi and iGlar was 60 units. Lixisenatide was self-administered once daily at a dose of 10 μg for the first 2 weeks, followed by 20 μg for the remainder of the study. For the purpose of this retrospective analysis, data from patients ≥65 years old from the LixiLan-L and -O trials were analyzed and compared with data from patients aged <65 years.

2.2. Efficacy and safety endpoints

Efficacy endpoints were changes from baseline in A1C, FPG, and PPG (2-h PPG levels were measured using a standardized meal challenge),[14,15] the proportion of patients achieving A1C goal (<7.0% [53 mmol/mol]), and change in body weight. Safety measures assessed were the incidence of documented symptomatic hypoglycemia (defined as typical symptoms of hypoglycemia accompanied by an SMPG value of ≤70 mg/dL [3.9 mmol/L]) or severe hypoglycemia (defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions) and the incidence of gastrointestinal AEs (nausea, vomiting and diarrhea). The percentage of patients achieving A1C <7.0% (53 mmol/mol) with no weight gain and no documented symptomatic hypoglycemia was also assessed.

Analysis variables were as follows: baseline value, end of study value (Week 30 last observation carried forward), and change from baseline to end of study value for efficacy endpoints; incidence rate on study treatment for all safety outcomes; and exposure-adjusted rates for documented symptomatic hypoglycemia.

2.3. Statistical analysis

A modified intent-to-treat population, consisting of all patients with post-baseline measurements as randomized, was used for efficacy measures. A safety population, consisting of all patients with post-baseline

measurements as treated, was used for safety measures. Descriptive statistics included number (n), mean, and standard deviation by treatment and age group, as well as incidence and rates for response and safety parameters.

Efficacy analyses of continuous variables are based on a two-way analysis of variance (ANOVA) means model including treatment and age subgroup as factors with single degree-of-freedom contrasts between iGlarLixi and comparators by subgroup and between subgroups. Analyses of discrete response variables are based on Cochran–Mantel–Haenszel tests for comparisons between iGlarLixi and comparators by subgroup and between subgroups. Safety analyses are based on chi-square tests (or Fisher exact tests for small frequencies) for treatment and age group comparisons.

3. Results

Among the 534 patients aged ≥65 years in the LixiLan-L and LixiLan-O trials, the majority of patients were between ≥65–69 years old (122 patients in the LixiLan-L trial and 175 patients in the LixiLan-O trial) (Supplemental Table S1).

Baseline A1C, PPG, and weight were similar between treatment groups and studies (Supplemental Table S1). FPG was similar for treatment groups within trials but was higher in the LixiLan-O trial than in the LixiLan-L trial (Supplemental Table S1). Patients aged ≥65 years generally had higher baseline FPG and PPG and lower weight than those aged <65 years (Supplemental Table S1).

3.1. Efficacy

In both trials, patients ≥65 years old treated with iGlarLixi achieved significantly greater reductions in A1C at Week 30 compared with iGlar (Table 1). In the LixiLan-O trial, patients treated with iGlarLixi also achieved significantly greater reductions in A1C at Week 30 compared with lixisenatide. A1C reductions were comparable among patients aged ≥65 and those aged <65 years (Table 1 and Supplemental Table S2).

For patients ≥65 years in the LixiLan-L trial, greater A1C reductions were seen in iGlarLixi-treated patients compared with iGlar-treated patients at all time points post baseline (A1C levels of 7.3% vs. 7.7% [56 mmol/mol vs. 61 mmol/mol] at Week 8; 7.1% vs. 7.7% [54 mmol/mol vs. 61 mmol/mol] at Week 12; 6.9% vs. 7.6% [52 mmol/mol vs. 60 mmol/mol] at Week 24; and 7.0% vs. 7.6% [53 mmol/mol vs. 60 mmol/mol] at Week 30 for iGlarLixi and iGlar, respectively) (Supplemental Fig. S1A). Results for patients ≥65 years in the LixiLan-O trial followed a similar pattern: baseline A1C levels were similar in all treatment groups, and the largest A1C reductions occurred in iGlarLixi-treated patients, followed by iGlar- and lixisenatide-treated patients at all time points post baseline (A1C levels of 7.1%, 7.4%, and 7.5% [54 mmol/mol, 57 mmol/mol, and 59 mmol/mol] at Week 8; 6.7%, 7.2%, and 7.4% [50 mmol/mol, 55 mmol/mol, and 57 mmol/mol] at Week 12; 6.5%, 7.0%, and 7.2% [48 mmol/mol, 53 mmol/mol, and 55 mmol/mol] at Week 24; and 6.5%, 6.9%, and 7.2% [48 mmol/mol, 52 mmol/mol, and 55 mmol/mol] at Week 30 for iGlarLixi, iGlar, and lixisenatide, respectively) (Supplemental Fig. S1B). A1C results over time among those aged <65 years (Supplemental Fig. S1C and D) were comparable to those from the older patients. Consistent with the reductions in A1C levels, there was a reduction in mean daily plasma glucose as measured by average SMPG in both the LixiLan-L and LixiLan-O trials (Table 1). The estimated treatment difference in A1C for iGlarLixi vs. iGlar was greater in insulin-experienced patients (Table 1).

In each study, significantly greater proportions of patients ≥65 years old, treated with iGlarLixi achieved target A1C <7.0% (53 mmol/mol) at Week 30 compared with either iGlar or lixisenatide (Fig. 1A). Overall, the proportion of patients achieving A1C <7.0% at Week 30 with both iGlarLixi and iGlar was higher in insulin-naive vs. insulin-experienced patients (78.0% and 54.4% [insulin-naive] vs. 51.8% and 21.0% [insulin-experienced] for iGlarLixi and iGlar, respectively). Compared with those treated with iGlar, patients treated with iGlarLixi, regardless of their prior insulin status, were significantly more likely to achieve the composite endpoint of A1C <7.0% (53 mmol/mol) with no weight gain and no documented symptomatic hypoglycemia (30.1% vs. 14.0% [$P = 0.002$; insulin-naive] and 26.4% vs. 8.4% [$P < 0.001$; insulin-experienced] for iGlarLixi and iGlar, respectively) (Fig. 1B). Results among those aged <65 years were generally similar to those in the older patients, although significantly fewer iGlar-treated patients ≥65 years in the LixiLan-L trial reached an A1C <7.0% compared to those <65 years (Supplemental Fig. S2).

Patients ≥65 years old treated with iGlarLixi also achieved significantly greater reductions in PPG levels at Week 30 compared with iGlar in both trials (−94.4 mg/dL vs. −24.1 mg/dL [$P < 0.001$; LixiLan-L] and −113.0 mg/dL vs. −64.2 mg/dL [$P < 0.001$; LixiLan-O] for iGlarLixi and iGlar, respectively) (Table 1). PPG reductions were

Table 1
Mean change by treatment for patients aged ≥65 years in the LixiLan-L and LixiLan-O trials.

	LixiLan-L		LixiLan-O		
	iGlarLixi (n = 110)	iGlar (n = 119)	iGlarLixi (n = 132)	iGlar (n = 114)	Lixisenatide (n = 58)
		n = 118			
A1C, %, mean (SD)	−1.11 (0.89)	−0.48 (0.84)	−1.45 (0.86)	−1.15 (0.79)	−0.90 (0.96)
Treatment difference vs. iGlarLixi, mean (SE)	–	0.63 (0.12)	–	0.30 (0.11)	0.55 (0.14)
P value	–	<0.001	–	0.007	<0.001
		n = 118			n = 57
FPG, mg/dL, mean (SD)	−8.5 (42.0)	−17.8 (48.5)	−62.9 (43.2)	−65.2[a] (48.5)	−37.4[a] (41.3)
Treatment difference vs. iGlarLixi, mean (SE)	–	−9.4 (6.5)	–	−2.3 (6.1)	25.6 (7.6)
P value	–	0.14	–	0.709	0.001
	n = 98	n = 115	n = 123	n = 107	n = 47
2 h PPG, mg/dL, mean (SD)	−94.4 (87.6)	−24.1 (70.2)	−113.0 (78.9)	−64.2 (70.1)	−93.2 (69.2)
Treatment difference vs. iGlarLixi, mean (SE)	–	70.3 (10.8)	–	48.8 (9.4)	19.8 (12.2)
P value	–	<0.001	–	<0.001	0.106
	n = 98	n = 106	n = 113	n = 100	n = 49
Average 7-point SMPG, mg/dL, mean (SD)	−29.7 (35.0)	−6.9 (33.8)	−56.9 (40.1)	−45.0 (39.4)	−42.3 (44.9)
Treatment difference vs. iGlarLixi, mean (SE)	–	22.8 (4.7)	–	11.9 (5.4)	14.6 (6.7)
P value		<0.001	–	0.027	0.029
Weight, kg, mean (SD)	−1.2[a] (2.8)	0.6 (2.5)	−0.9[a] (3.7)	1.2 (3.0)	−2.0 (3.5)
Treatment difference vs. iGlarLixi, mean (SE)	–	1.8 (0.4)	–	2.2 (0.5)	−1.1 (0.6)
P value	–	<0.001	–	<0.001	0.074

A1C, glycated hemoglobin A1C; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; SD, standard deviation; SE, standard error; SMPG, self-measured plasma glucose.
[a] Significant difference versus those aged <65 years (see Supplemental Table S2).

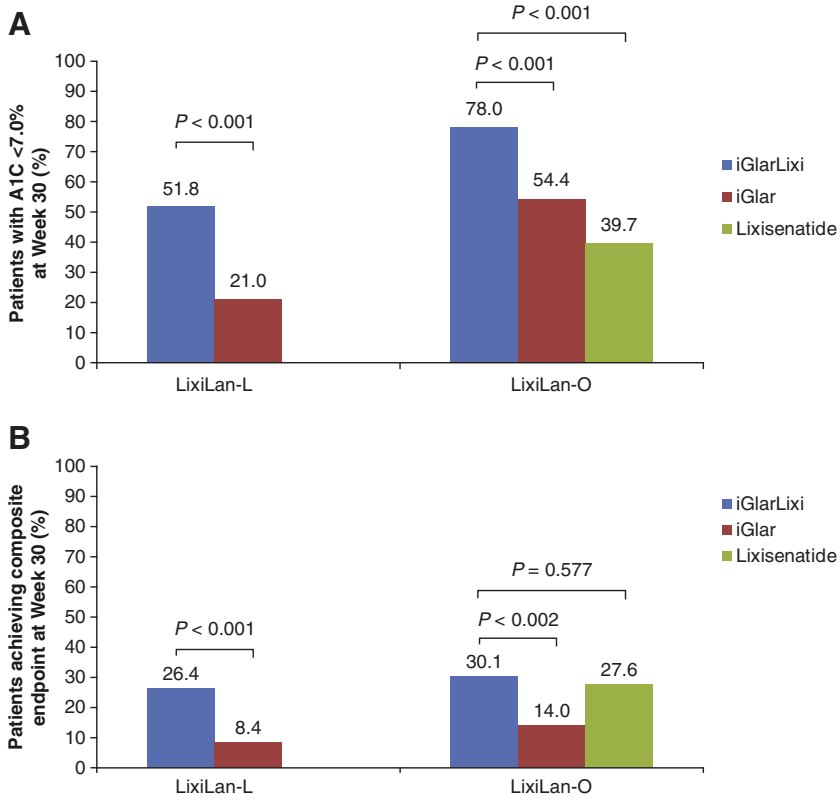

Fig. 1. Percentage of patients aged ≥65 years in the LixiLan-L and LixiLan-O trials who after 30 weeks achieved (A) A1C <7.0% (53 mmol/mol) at Week 30 of treatment in the LixiLan-L and LixiLan-O trials or (B) composite endpoint of A1C <7.0% (53 mmol/mol), with no weight gain and no documented symptomatic hypoglycemia.

comparable between those aged <65 years (Supplemental Table S2) and those aged ≥65 years (Table 1).

Treatment with iGlarLixi was associated with reductions in body weight from baseline, including a significant reduction in weight from baseline compared with iGlar in both studies (−1.2 kg vs. +0.6 kg [$P < 0.001$; LixiLan-L] and −0.9 kg vs. +1.2 kg [$P < 0.001$; LixiLan-O] for iGlarLixi and iGlar, respectively) (Table 1). In the LixiLan-O trial, iGlarLixi was associated with a smaller, non-significant reduction in

Table 2
Safety outcomes for patients aged ≥65 years in the LixiLan-L and LixiLan-O trials.

	LixiLan-L		LixiLan-O		
	iGlarLixi (n = 110)	iGlar (n = 119)	iGlarLixi (n = 133)	iGlar (n = 114)	Lixisenatide (n = 58)
Discontinuation due to AEs, %	6.4	0.0	3.0	1.8	8.6
Treatment difference vs. iGlarLixi, (SE)	–	−6.4 (2.4)	–	−1.3 (1.9)	5.6 (4.0)
Documented symptomatic hypoglycemia[a]					
Patients with events, %	36.4	43.7	27.8	28.9	3.4
Treatment difference vs. iGlarLixi, (SE)	–	6.7 (6.4)	–	0.9 (5.8)	−24.9 (4.7)
Events/patient-year	2.84	4.91	1.42	1.89	0.24
Treatment difference vs. iGlarLixi, (SE)	–	2.07 (0.35)	–	0.46 (0.22)	−1.19 (0.17)
Severe hypoglycemia					
Patients with events, %	1.82	0.00	0.00	0.88	0.00
Treatment difference vs. iGlarLixi, (SE)	–	−1.82 (0.01)	–	0.88 (0.02)	0.00 (0.00)
Events/patient-year	0.03	0.00	0.00	0.02	0.00
Treatment difference vs. iGlarLixi, (SE)	–	−0.03 (0.02)	–	0.02 (0.02)	0.00 (0.00)
Gastrointestinal AEs, %					
Nausea	13.6	0.8	12.0	2.6	20.7
Treatment difference vs. iGlarLixi, (SE)	–	−12.8 (3.6)	–	−9.4 (3.3)	8.8 (5.8)
Vomiting	3.6	0.8	4.5	1.8	6.9
Treatment difference vs. iGlarLixi, (SE)	–	−2.9 (2.3)	–	−3.0 (2.4)	2.6 (4.1)
Diarrhea	7.3	2.5	9.0	6.1	8.6
Treatment difference vs. iGlarLixi, (SE)	–	−4.4 (2.9)	–	−2.8 (3.5)	−0.7 (4.4)
Discontinuation due to gastrointestinal AEs, %	2.7	0.0	1.5	0.0	5.2
Treatment difference vs. iGlarLixi, (SE)	–	−2.7 (1.7)	–	−1.5 (1.1)	3.7 (3.1)

AE, adverse event; SE, standard error; SMPG, self-measured plasma glucose.
[a] Documented symptomatic hypoglycemia, defined as typical symptoms of hypoglycemia accompanied by an SMPG value of ≤70 mg/dL (3.9 mmol/L).

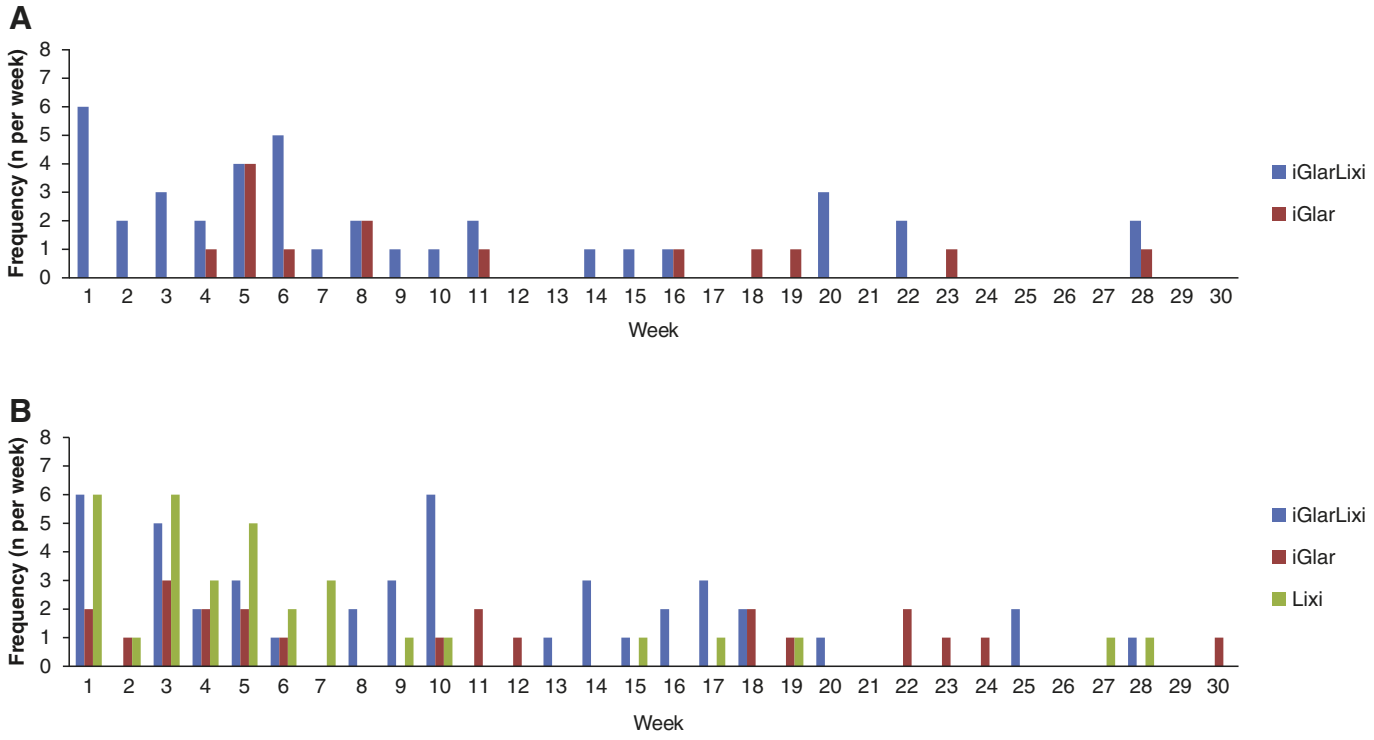

Fig. 2. Frequency of onset of gastrointestinal side effects from Week 1 to Week 30 in patients aged ≥65 years in (A) the LixiLan-L trial and (B) the LixiLan-O trial.

weight compared with lixisenatide (−0.9 kg vs. −2.0 kg for iGlarLixi and lixisenatide, respectively [$P = 0.074$]) (Table 1). Weight reductions with iGlarLixi were significantly smaller among those aged <65 years (Supplemental Table S2) vs. those aged ≥65 years; however, this difference was not clinically meaningful (Table 1).

3.2. Safety

In the LixiLan-L trial, the percentage of patients with documented symptomatic hypoglycemia was comparable between iGlarLixi and iGlar (Table 2). In contrast, the documented hypoglycemia event rates per patient-year were substantially lower in patients with iGlarLixi compared with iGlar (Table 2).

Similarly, the percentage of patients in the LixiLan-O trial who experienced documented symptomatic hypoglycemia was comparable for patients treated with iGlarLixi vs. iGlar (Table 2), and the documented hypoglycemia event rates per patient-year were also slightly lower with iGlarLixi as compared with iGlar (Table 2).

Compared with lixisenatide alone, iGlarLixi was associated with a higher incidence of documented symptomatic hypoglycemia and with higher event rates of hypoglycemia per patient-year (Table 2).

In both trials, the percentage of patients with severe hypoglycemia and the event rates of severe hypoglycemia did not differ between patients treated with iGlarLixi vs. iGlar (Table 2). There were no notable trends in hypoglycemia rates (documented symptomatic or severe) by age group (Table 2 and Supplemental Table S3).

The proportion of patients experiencing gastrointestinal side effects was greater with iGlarLixi than with iGlar in both studies but considerably lower than was documented for lixisenatide (Table 2). In both trials, the frequency of gastrointestinal side effects generally decreased over time for iGlarLixi and lixisenatide (Fig. 2). Discontinuation rates due to gastrointestinal AEs for iGlarLixi and lixisenatide-treated patients were low (Table 2). Similar gastrointestinal AE patterns were observed among those aged <65 years (Supplemental Table S3 and Fig. S3). However, iGlarLixi-treated patients aged <65 years were somewhat less likely to experience gastrointestinal AEs than those aged ≥65 years (Supplemental Table S3 and Table 2).

In the LixiLan-O trial, AEs leading to permanent treatment discontinuation were reported by a similar percentage of patients in the iGlarLixi (3.0% [3/133]) and iGlar (1.8% [2/114]) groups, whereas the percentage was higher in the lixisenatide group (8.6% [4/58]) (Table 2). In the LixiLan-L trial, more patients treated with iGlarLixi discontinued treatment vs. iGlar (6.4% [7/110] vs. 0.0% for iGlarLixi and iGlar, respectively) (Table 2). Patients aged <65 years were less likely to discontinue iGlarLixi than those aged ≥65 years in the LixiLan-L trial. This difference was likely to be driven by the slightly higher rates of nausea in iGlarLixi-treated patients ≥65 years. This was not seen in the LixiLan-O trial (Supplemental Table S3 and Table 2).

4. Discussion

In patients aged ≥65 years, iGlarLixi was consistently more effective than iGlar in improving glycemic control by lowering A1C and PPG, without increasing the risk of hypoglycemia. Despite some baseline differences between patients aged ≥65 years and those aged <65 years, iGlarLixi showed superior reductions in A1C, PPG and composite endpoints compared with iGlar in both age groups. Safety endpoints were also comparable between the age groups, with slightly more weight loss and gastrointestinal AEs in older than younger patients; however, gastrointestinal AEs remained considerably attenuated with iGlarLixi compared with lixisenatide alone. Overall, treatment with iGlarLixi allowed more patients to achieve glycemic control while mitigating insulin-related weight gain and GLP-1 RA-related gastrointestinal AEs.

Guidelines for the management of diabetes in older adults do not depend on age alone but mirror those for the general population in recommending individualized therapy — this includes setting glycemic targets based on the burden of comorbidities, functional status, and life expectancy, as well as considering the effect of treatment on hypoglycemia risk and weight when making treatment choices.[4,6,7]

It is advisable that agents with a lower risk of hypoglycemia are considered for older patients trying to achieve glycemic goals:

hypoglycemia is of particular concern in this population, because it is often overlooked or not reported to clinicians.[16] Severe hypoglycemia in general is associated with a range of serious acute vascular events and mortality[16–18] and, especially in older patients, an increase in the risk of dementia.[19] Recurrent episodes of milder hypoglycemia can also have significant negative consequences (including functional, physical, and cognitive decline) and can increase the risk of falls and fractures and cause a worsening of cardiovascular disease, dementia, frailty, and disability.[16,17] Therefore, when choosing treatment for older patients with type 2 diabetes, balancing the benefits of glycemic control against the potential harms and burdens of treatment is of particular importance.

In the current study, the number of documented symptomatic hypoglycemia events per patient-year was generally low overall, and it was considerably lower for iGlarLixi (compared with iGlar) in patients aged ≥65 years in the LixiLan-L and LixiLan-O studies. This was despite the fact that iGlarLixi achieved significantly greater reductions in A1C and lower A1C at all time points up to Week 30 compared with iGlar. These findings suggest that it may be possible to effectively achieve glycemic control in older patients without increasing the risk of hypoglycemia.

These results are supported by findings from the GetGoal-O study, which demonstrated that the addition of lixisenatide to existing BI treatment ± OADs in patients ≥70 years with type 2 diabetes and inadequate glycemic control resulted in significant reductions in A1C, PPG, and body weight.[20] Consistent with the other trials, the events per patient-year of documented symptomatic hypoglycemia (BG <70 mg/dL) in patients who added lixisenatide to existing BI ± OADs were comparable with those who added placebo (0.29 vs. 0.37 events/patient-year; data on file). Although the absolute symptomatic hypoglycemia events per patient-year vary across the different studies, they are consistently lower for iGlarLixi or lixisenatide on a background of BI as compared with iGlar in patients uncontrolled on either OADs or BI (1.42 vs. 1.89 events/patient-year [LixiLan-O] and 2.84 vs. 4.91 events/patient-year [LixiLan-L]).

Weight gain is a well-known issue associated with antidiabetic therapies (BIs included).[6,21] Avoidance of weight gain is a well-established principle in the treatment of patients (including older patients) with type 2 diabetes, and guidelines recommend that regimens favoring weight control be used where possible.[4,6] In both LixiLan trials, treatment with iGlar led to weight gain, whereas treatment with iGlarLixi mitigated that effect, with patients in both studies experiencing slight reductions in weight vs. baseline. The improvements in glycemic control experienced by most patients (vs. iGlar), along with the accompanying weight loss and a lower rate of symptomatic hypoglycemia, suggest that iGlarLixi may represent a particularly beneficial treatment intensification strategy in older patients with type 2 diabetes.

Nausea and other gastrointestinal AEs are common with GLP-1 RAs, and they are a common cause for treatment discontinuation.[15,22,23] In addition, the occurrence of gastrointestinal AEs is generally greatest in the first 60 days of treatment initiation.[24] Older patients treated with iGlarLixi in the LixiLan-O trial had lower rates of nausea and vomiting compared with those treated with lixisenatide. The lower incidence of gastrointestinal AEs with iGlarLixi (vs. lixisenatide) is likely due to the more gradual dose escalation and overall lower mean dose of lixisenatide when taken as part of the titratable fixed-drug combination (iGlarLixi).

In general, treatment discontinuation resulting from AEs was found to vary between the LixiLan-L and LixiLan-O trials. In the LixiLan-O trial, treatment discontinuation was highest in the lixisenatide group, whereas discontinuation was reported by a similar percentage of patients in the iGlarLixi and iGlar groups. By contrast, in the LixiLan-L trial, more patients treated with iGlarLixi discontinued treatment compared with patients treated with iGlar. It is important to note that the low overall discontinuation rates in both trials did not affect the final outcomes.

Polypharmacy in older patients with type 2 diabetes, with the need to take multiple agents over the course of the day, is a growing concern that has been linked to negative consequences or conditions, including an increased incidence of hypoglycemia, adverse drug events, drug–drug interactions, non-adherence to medication, functional decline, cognitive impairment, and decreased quality of life.[25–27] Another issue of importance for older adults is treatment complexity. More complex regimens may undermine adherence, as well as introduce opportunities for medication error. iGlarLixi offers the benefit of being a once-daily injection, which may simplify the treatment regimen for patients who are likely using multiple treatments. It may therefore be of particular benefit in older patients and potentially improve patient adherence and outcomes.

The main limitation of this analysis was its post hoc nature. The LixiLan-L and LixiLan-O trials were not specifically designed to assess an older adult population. Although not excluded on the basis of age alone, some older patients were not included in the trials due to the exclusion criteria included in the LixiLan trials (e.g., history of hypoglycemia unawareness and certain comorbidities).

This analysis provides important insights and adds to our knowledge of lixisenatide use in older type 2 diabetes populations (both in combination with iGlar as iGlarLixi and when used alone). The findings of this analysis suggest that, compared with iGlar, which mainly targets FPG, the complementary mechanism of action of iGlarLixi on both PPG and FPG results in improved glycemic control without increased risk of hypoglycemia in older patients. Regardless of age, treatment with iGlarLixi has been shown to mitigate insulin-related weight gain and lixisenatide-related gastrointestinal AEs.

5. Conclusions

The titratable fixed-ratio combination iGlarLixi provides significant improvements in glycemic control in patients aged ≥65 years – comparable with patients aged <65 years – without increasing hypoglycemia risk. As a once-daily injection, it provides a simplified treatment approach for older patients and may contribute to improved adherence in this patient population.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jdiacomp.2018.11.009.

Acknowledgments

The authors received writing/editorial support in the preparation of this manuscript provided by Catarina Fernandes, PhD, and Ila Karve, PhD, of Excerpta Medica, funded by Sanofi US, Inc.

Funding

This study and the writing/editorial support were sponsored by Sanofi.

Author contributions

Y.H. contributed to data analysis and critical revision of the manuscript. C.C. contributed to data analysis and critical revision. T.D. contributed to study design, data analysis and critical revision. F.G. contributed to data analysis and critical revision. N.S. contributed to data analysis and critical revision. E.S. contributed to study design, data analysis and critical revision. W.S. contributed to data acquisition, data analysis and critical revision. E.N. contributed to data analysis and critical revision. J.F. contributed to data analysis and critical revision. All authors are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics approval and consent to participate

The study was designed and monitored in accordance with Good Clinical Practice, the International Conference on Harmonization, and the Declaration of Helsinki. Institutional review boards or ethics committees at each study site approved the protocol. Each patient gave written informed consent.

Consent for publication

The contents of the paper and the opinions expressed within are those of the authors, and it was the decision of the authors to submit the manuscript for publication.

Availability of data and material

The data that support the findings of this study are available from Sanofi but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

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