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MINI REVIEW

Insulin Efsitora a Useful Addition to Treatment of Type 2 Diabetes but not Type 1 Diabetes

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Abstract

Efsitora is a once-weekly basal insulin under investigation in a series of 5 phase 3 clinical trials called the QWINT development program. In QWINT-2 and QWINT-5 trials including insulin-naive patients with type 2 diabetes and adults with type 1 diabetes, respectively, efsitora was compared to once-daily degludec. In both trials, efsitora was found non inferior to degludec in lowering glycated hemoglobin (HbA1c) levels after 52 weeks. In patients with type 2 diabetes, 6 episodes of level 3 hypoglycemia (i.e. severe hypoglycemia associated with cognitive impairment) occurred with degludec versus none with efsitora. However, incidence of level 1 hypoglycemia or hypoglycemia alert [blood glucose (BG) 54-69 mg/dl] was numerically greater with efsitora versus degludec, estimated rate ratio (ERR) 1.24 (95% CI, 0.99-1.55). Moreover, rates of level 2 hypoglycemia or clinically significant hypoglycemia (BG <54 mg/dl) were also numerically increased with efsitora versus degludec, ERR 1.34 (0.94-1.78). In type 1 diabetes, the QWINT-5 study showed that incidence of all levels of hypoglycemia was significantly increased with efsitora versus degludec, with relative rates of 1.15 (95% CI, 1.03-1.29; P=0.016) and 3.44 (95% CI, 1.64-7.19; P=0.0011) for levels 1 and 3 hypoglycemia, respectively. Incidence of nocturnal hypoglycemia was similar in efsitora and degludec groups in both QWINT-2 and QWINT-5 trials. Patients' satisfaction was significantly improved with efsitora versus degludec in patients with type 1 and type 2 diabetes. In conclusion, efsitora might be a convenient basal insulin for patients with type 2 diabetes to decrease number of insulin injections. However, efsitora may be unsafe in patients with type 1 diabetes due to increased risk of hypoglycemia. Further studies are required to determine a safe dose-titration strategy to decrease incidence of hypoglycemia with efsitora.

Key Words: *Efsitora; Icodec; Once-weekly insulin; Glycated hemoglobin; Hypoglycemia.*

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Introduction

In an attempt to decrease burden of insulin injections, 2 once-weekly insulin formulations were introduced: icodec and efsitora [1,2]. Icodec (trade name Awikli) was recently approved by the European Union (EU), Canada and Switzerland for treatment of adults with diabetes [3]. Meanwhile, icodec was rejected by the Federal Drug Administration (FDA) in the USA due to increased risk of hypoglycemia [3]. Efsitora (code LY3209590) also known as basal insulin Fc (BIF), is another once-weekly basal insulin that consists of a single chain variant insulin fused to a human immunoglobulin G2 (IgG2) fragment crystallizable (Fc) domain [4]. Main differences between icodec and ifsitora are depicted in table 1. Efsitora provides a stable insulin plasma levels with little variability as reflected by its low peak-to-trough ratio of 1.14 [4]. The latter is defined as the ratio of the highest and lowest plasma concentration at steady state [4]. Efsitora has a prolonged half-life of approximately 17 days [4]. There are 2 main factors contributing to the long half-life of efsitora. First, efsitora has reduced affinity to insulin receptor leading to its decreased rate of clearance. Thus, efsitora exhibits approximately 130-fold decreased binding affinity to insulin receptor compared to native insulin [5]. Second, fusion of efsitora with the Fc domain protects it from elimination by pinocytosis [2]. Efsitora is currently under investigation in 5 phase 3 trials called the QWINT program (QW Insulin Therapy) [6]. Two of the 5 trials have been published, the QWINT-2 and QWINT-5 trials in type 2 and type 1 diabetes, respectively [7,8]. Overview of the QWINT-2 and QWINT-5 trials is summarized in table 2. The main purpose of this review is to provide an appraisal of efsitora as a new once-weekly basal insulin.

TABLE 1

Comparison between the 2 weekly insulins icodec and efsitora.

	Icodec [1]	Efsitora [2,3]
Structure		Single-chain insulin variant combined with a human IgG2 Fc domain
Half-life	8.1 days	17 days
Approval status	Approved for adults with type 1 and type 2 diabetes in EU, Switzerland, Canada under the name “Awiqli [Blair],	Under development in phase 3 program
Glycemic efficacy	Non-inferior or slightly superior to degludec and glargine (HbA1c difference approximately 0.2%)	Non-inferior to degludec
Incidence of hypoglycemia	Higher than glargine and degludec, particularly in type 1 diabetes. No increase in nocturnal hypoglycemia	Higher than degludec, particulary in type 1 diabetes. No increase in nocturnal hypoglycemia

Abbreviations: IgG2Fc: immunoglobulin G2 (IgG2) fragment crystallizable (Fc), HbA1c: glycated hemoglobin.

TABLE 2
Overview of QWNIT-2 and QWINT-5 trials.

	QWINT- 2 [7]	QWINT-5 [8]
Design	Randomized, open-label, multinational, 2 groups, non-inferiority, 52 weeks	Randomized, open-label, multinational, 2 groups, non-inferiority, 52 weeks
Disease	Type 2 diabetes, insulin-naive	Type 1 diabetes on basal and short-acting insulin
Intervention	Efsitora once-weekly versus degludec once-daily	Efsitora once-weekly versus degludec once-daily
Duration of diabetes (years)	11.6	17.4
Patients' characteristics	N= 928, 57 years-old, 59% males, 50% Whites, 35% Asians	N= 893, 44 years-old, 55% males, 75% Whites, 21% Asians
Baseline HbA1c 8.2% 7.9%		
Body weight (kg)	86.5	75.5
BMI (kg/m2)	30.6	26.2
Primary outcome	Non-inferiority of efsitora to degludec with respect to change in HbA1c from baseline to week 52	Non-inferiority of efsitora to degludec with respect to change in HbA1c from baseline to week 26
Fasting blood glucose target	80-120 mg/dl	80-120 mg/dl
Continuous glucose monitoring	Worn "intermittently" during the trial	CGM worn throughout the whole trial
Loading dose of efsitora	300 units	Usual daily basal dose x7 (rounded to the nearest 10) then multiplied by 3.

Values are means. Abbreviations; HbA1c: glycated hemoglobin, BMI; body mass index

Glycemic efficacy of efsitora in type 2 diabetes

The QWINT-2 trial compared subcutaneous once-weekly efsitora (n=466) with once-daily degludec (n=462) in insulin-naïve patients with type 2 diabetes (Table 2) [7]. The first dose of efsitora (500 U/ml) was a loading dose of 300 U to accelerate reaching efficacious plasma levels. For the second week, patients received a starting dose of efsitora of 100 U once per week [7]. Participants in the degludec group started with 10 U daily. Subsequently, dose adjustments in an open-label fashion was done to achieve a target fasting BD of 80-120 mg/dl [7]. After 52 weeks of intervention, efsitora was non-inferior to degludec in lowering HbA1c levels. Thus, mean reductions of glycated hemoglobin values were -1.26 percentage points (from 8.21% to 6.97%) and -1.17 percentage points (from 8.24% to 7.05%) in the efsitora and degludec groups, respectively [7]. In both groups, maximum decrease in glycated hemoglobin levels occurred at approximately 16 weeks followed by a plateau [7]. Total weekly dose at week 52 was significantly lower in efsitora 314.7 units/week (45.0 units/d) versus 334.4 units/week (47.8 units/day) with degludec, estimated difference -19.7 units/week; 95% CI (-37.0 to -2.4) [7].

Glycemic efficacy of efsitora in type 1 diabetes

The QWINT-5 trial compared once-weekly efsitora (n=343) with once-daily degludec (n=349) in adult patients with type 1 diabetes (Table 2) [8]. The first loading dose of efsitora was the pre-trial basal insulin dose multiplied by 7 (rounded to the nearest 10), and then multiplied by 3 [8]. Subsequent efsitora doses were the pre-trial basal insulin doses multiplied by 7 and rounded to the nearest 10 [8]. In the degludec group, the starting degludec doses were equivalent to the pre-study doses. In both groups, bolus insulin was lispro given in the same pre-study doses [8]. During the trial, insulin doses were adjusted based on target fasting blood of 80-120 mg/dl. Efsitora was non-inferior to degludec in lowering HbA1c levels. The latter were decreased by -0.51 and -0.61 percentage after 26 weeks with efsitora and degludec, respectively difference nonsignificant 0.052%, P=0.43) [8]. After 52 weeks, HbA1c values were 7.5% in both groups [8]. Regarding time course of HbA1c values, in both arms, HbA1c levels reached a trough at 12 weeks then exhibited a mild rebound [8]. Basal insulin doses were similar at 52 weeks, 204.4 units/week (29.2 units/d) and 211.3 units/week (29.7 units/d) with efsitora and degludec, respectively [8].

Safety of efsitora

In type 2 diabetes, serious adverse effects were reported in 8.8% and 8.2% in patients with efsitora and degludec, respectively [7]. However, in the trial of type 1 diabetes, serious adverse effects were more common with efsitora (13% versus degludec 7%, mainly due to more frequent events of level 3 hypoglycemia in the efsitora group (see below) [8].

Hypoglycemia in type 2 diabetes

No severe (level 3) episodes of hypoglycemia occurred with efsitora but 6 cases were reported with degludec, 5 of whom were receiving sulfonylureas [7]. However, rates of level 1 hypoglycemia (hypoglycemia alert) were numerically increased with efsitora, ERR 1.24 (95% CI, 0.99-1.55). Moreover, rates of clinically significant level 2 hypoglycemia were also numerically increased with efsitora versus degludec, ERR 1.34 (0.94-1.78) [7]. Meanwhile, rates of nocturnal hypoglycemia were similar in both groups, ERR 1.01 (95% CI, 0.53 to 1.89) [7].

Hypoglycemia in type 1 diabetes

In patients with type 1 diabetes, the incidence of level 3 hypoglycemia was significantly higher with efsitora compared with degludec occurring in 10% (35 of 343) and 3% (11 of

349), respectively [8]. In fact, from study entry to week 52, 44 events of level 3 or severe hypoglycemia occurred with efsitora versus 13 events with degludec, estimated relative rate 3.44 (95% CI, 1.64 to 7.19; P=0.001) [8]. Most episodes of severe hypoglycemia (64%) with efsitora occurred during the initial 12-week titration period [8]. In addition, 2 patients went into hypoglycemic coma in the efsitora group [8]. Rates of level 2 or clinically significant hypoglycemia were not reported separately in the QWINT-5 study. Yet, the authors reported that rates of combined level 2 or level 3 hypoglycemia were also significantly increased with efsitora versus degludec, estimated relative rate 1.21 (95% CI, 1.04 to 1.41; P=0.016) [8]. Finally, rates of level 1 hypoglycemia were higher with efsitora than degludec 39.1 and 33.9 patient-year exposure, respectively; estimated relative rate 1.15 (95% CI, 1.03 to 1.29; P=0.016) [8]. Interestingly, metrics derived from continuous glucose monitoring showed similar duration of combined level 1 (<70 mg/dl) and level 2 hypoglycemia (<54 mg/dl) in the efsitora and degludec group. Likewise, nocturnal hypoglycemia (levels 2 and 3) were similar in the 2 insulin groups [8]. Importantly, like in patients with type 2 diabetes in the QWINT-2 trial, incidence of nocturnal hypoglycemia with efsitora was not increased compared to degludec, possibly due to the low peak-to through ratio of efsitora which correlates with decreased nocturnal hypoglycemia [4]. It was somewhat reassuring that there were no prolonged episodes of hypoglycemia reported with efsitora in both type 1 and type 2 diabetes trials [7,8]. Prolonged or repeated hypoglycemia was a potential concern of efsitora in view of its long duration of action.

Injection site reactions

Injections site reactions were numerically more common with efsitora versus degludec (9 versus 1 patient with type 1 diabetes and 11 versus 8 patients with type 2 diabetes [7,8].

Moderate hypersensitivity events were higher with efsitora versus degludec in type 2 diabetes (2.6% versus 1.3%), but similar in the trial of type 1 diabetes [7,8].

Advantages of efsitora

The biggest advantage of once weekly efsitora is the substantial reduction in frequency of insulin injections. This advantage was reflected by the significant positive changes in scores of the Treatment-Related Impact Measure-Diabetes (TRIM-D) in type 2 diabetes and diabetes satisfaction questionnaire in type 1 diabetes [7,8].

Limitations of efsitora

The strongest limitation of efsitora is increased incidence of hypoglycemia (except nocturnal), particularly in type 1 diabetes. The observation that most severe hypoglycemic episodes in patients with type 1 diabetes occurred during the initial titration phase suggests that less aggressive dose up-titration during that period could virtually decrease hypoglycemia risk. In a cross-over trial, Heise et al [9] compared frequency and patterns of hypoglycemic episodes of efsitora versus glargine in a group of patients with type 2 diabetes exposed to provocation of hypoglycemia by 3 tests: 24 h fasting, 24 h fasting + exercise and by double dosing of efsitora [9]. During the 3 provocations testing, frequency of level 2 hypoglycemia was higher with efsitora versus glargine. For example, during the 24 h-fasting, 6 of 47 participants (12.8%) receiving efsitora had level 2 hypoglycemia versus none of them when receiving glargine [9]. Fortunately, despite the long duration of action of efsitora, there was no evidence of prolonged duration of hypoglycemia compared to degludec [9].

Other limitations of efsitora were the multiple exclusion criteria that limit generalizability of results of QWINT-2 and QWINT-5 trials to real-world patients with type 2 and type 1 diabetes.

These exclusions included subjects with HbA1c > 10.0%, severe hypoglycemia within 6 months prior to screening, and hypoglycemia unawareness [7,8]. Although chronic kidney disease (CKD) was not an exclusion criterion, only 8.6% of patients in QWINT-2 trial had an estimated glomerular filtration rate < 60 ml/min/1.72 m^2 [7]. In the QWINT-5 trial of type 1 diabetes, baseline kidney function was not reported [8]. Therefore, the safety of efsitora has yet to be studied in the setting of CKD, a strong risk factor for hypoglycemia. Finally, the QWINT-2 and QWINT-5 trials were open-label and sponsored by the efsitora manufacturer [7,8]. Thus, likelihood of bias could not be excluded.

Clinical implications

Based on available data from the QWINT-2 trial, efsitora might be used as initial basal insulin in patients with type 2 diabetes to decrease frequency of injections in place of once daily basal insulins [7]. Because of a trend towards increased frequency of level 2 hypoglycemia in the QWINT-2 trial with efsitora, the author suggests very gradual up-titration of efsitora doses to avoid such adverse effect. In addition, use of efsitora should be avoided in patients with CKD until more safety data become available in this population. With respect to patients with type 1 diabetes, efsitora cannot be recommended due to significant increase in incidence of all levels of hypoglycemia as shown in the QWINT-5 trial [8].

Clinical challenges for use of efsitora

No doubt, clinicians will face many challenges when using efsitora. First, they must be familiar with its pharmacokinetics and necessity to give a loading dose upon its initiation. Second, switching from once-daily basal insulin to once weekly might be problematic. This switch is currently investigated in the QWINT-2 and QWINT-3 trials [6]. Third, the art of efsitora dose titration will require extreme caution to avoid hypoglycemia. Fourth, intense education should be offered to patients before starting efsitora to avoid dosing errors. In addition, patients and medical providers should be able to incorporate metrics of continuous glucose monitoring to optimize insulin dosing.

Conclusions and Current Needs

The once-weekly efsitora was similar in efficacy to the once-daily degludec in patients with type 1 and type 2 diabetes. However, frequency of hypoglycemia was higher with efsitora compared with degludec, particularly in type 1 DM. Before considering approval of efsitora, the problem of increased hypoglycemia should be resolved. Thus, further studies are needed using smaller loading doses of efsitora and less aggressive titration schedules in an attempt to lower incidence and severity of hypoglycemia. In the meantime, combination of efsitora with once-weekly glucagon receptor agonist 1 agonist both given as a single injection should be evaluated similar to current trials testing combination of insulin icodec with semaglutide. The ongoing QWINT-1, QWINT-3 and QWINT-4 should clarify the efficacy and safety of efsitora in patients with type 2 diabetes in comparison to glargine (QWINT-1 and QWINT-4) and degludec (QWINT-3). Efsitora should be evaluated in patients with poorly controlled diabetes with HbA1c > 10.0% and in patients with CKD. Finally, randomized trials of several-year duration are essential to evaluate the long-term safety and efficacy of efsitora and its effects on cardiovascular events and mortality.

Conflict of Interest

The author has no conflict of interest to declare.

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