Exenatide Once Weekly: Effectiveness, Tolerability, and Discontinuation Predictors in a Real-World Setting

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ABSTRACT

Purpose: The goal of this study was to evaluate the effectiveness and safety of exenatide once weekly (EOW) and to determine predictors of treatment response and drug discontinuation in patients with type 2 diabetes mellitus (T2DM) followed up for 18 months in a real-world setting.

Methods: This retrospective cohort study included patients with T2DM who initiated EOW 2 mg between 2014 and 2019 in an outpatient diabetes clinic in Italy. Data were collected at baseline and at follow-up visits (6, 12, and 18 months after EOW). We estimated glycosylated hemoglobin (HbA_{1c}) and body weight mean changes from baseline to follow-up visits and assessed the proportion of patients reaching HbA_{1c} target $\leq$7% and a 5% weight loss after 12 months of treatment. We then attempted to establish predictors of glycemic and weight response, and compared patient characteristics between subjects who persisted on treatment versus those who discontinued EOW.

Findings: One-hundred eighty-six patients (46.2% male) were included in the study. The mean (SD) age and diabetes duration were 63.2 (8.9) years and 10.7 years (18.3), respectively. Significant reductions in HbA_{1c} values (–0.9%; 95% CI, –1.1 to –0.8) and body weight (–2.8 kg; 95% CI, –3.4 to –2.2) were observed after 6 months. Sixty-one percent of patients (87 of 143) achieved target HbA_{1c} values $\leq$ 7% after 12 months, and 34% (45 of 134) exhibited a weight loss of at least 5% of baseline body weight. Blood glucose and weight reductions were maintained after an 18-month follow-up. Predictors of adequate glycemic and weight response were shorter diabetes duration and nonuse of a different GLP-1RA, respectively. Patients on sulfonylureas failed to reach metabolic and body weight targets. The most common adverse events were gastrointestinal side effects (7.5%) and injection site reactions (6.4%), followed by headache (1.1%) and allergic reactions (1.1%). Forty-three percent of patients (79 of 186) discontinued EOW. The main reasons for discontinuation were insufficient HbA_{1c} improvement and/or limited weight reduction (19.9%), side effects (16.1%), or patient decision (6.5%). Predictors of discontinuation were higher HbA_{1c} levels at baseline and use of basal insulin therapy before EOW treatment.

Implications: EOW treatment, in a real-world setting, offers sustained and effective glycemic control and weight loss over 18 months in patients with T2DM. Diabetes duration and basal insulin therapy, however, may affect the outcome of EOW treatment, suggesting that early initiation of EOW could improve glycemic control and reduce the risk of treatment discontinuation. (*Clin Ther*. xxxx;xxx:xxx) © 2020 Elsevier Inc.

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Key words: clinical practice, exenatide once weekly, real-world evidence, type 2 diabetes mellitus.

INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a class of molecules currently used as second-line treatment for type 2 diabetes (T2DM) after failure of one or more oral antidiabetic agents. GLP-1RAs improve glycemic control and induce a significant reduction in body weight with minimal risk of hypoglycemic events.[1,2] Moreover, based on CVOT (CardioVascular Outcome Trials) results, it is acknowledged that GLP-1RAs, as a class, protect patients with T2DM from adverse cardiovascular outcomes and slow the progression of albuminuria.[3,4] These characteristics make GLP-1RAs a valid choice in diabetes treatment and place them among the drugs that should always be used in patients with ascertained cardiovascular disease, as stated in the latest international guidelines for diabetes management.[5]

Unfortunately, despite the strong evidence supporting their efficacy and safety, use of GLP-1RAs is still relatively limited. In Italy, although >50% of patients with T2DM present with clinical features making them eligible for therapy with GLP-1RAs, only 3.7% are currently treated with drugs of this class.[6,7] This might be due to clinicians' resistance in relying solely on data gathered from randomized controlled clinical trials. Data obtained in actual clinical practice might help in reassuring clinicians about the effectiveness, safety, and ease of use of this class of drugs in a real-world setting.

In addition to efficacy and safety, drug tolerability and ease of administration are 2 important issues driving therapeutic choices in clinical practice. As known, all GLP-1RAs are associated with gastrointestinal side effects, including nausea, vomiting, and diarrhea. Injection site reactions (eg, erythema, pruritus, nodules) may also occur, mainly in the initial phase of treatment, with their incidence decreasing over time.[8,9] A simplified dosing regimen also represents a useful strategy to improve treatment adherence to medication.[10]

Exenatide once weekly (EOW) is a long-acting formulation of a GLP-1RA, administered once weekly and able to significantly improve glycemic control in patients with T2DM. The efficacy, safety, and tolerability of EOW were evaluated in the Phase III studies of the Diabetes Therapy Utilization: Researching Changes in A1C, Weight and Other Factors Through Intervention with Exenatide Once Weekly (DURATION) trial program. In these studies, reductions in glycosylated hemoglobin (HbA_{1c}) from 1.3% to 1.9% and weight reductions of ~2−4 kg from baseline were observed.[11,12] The metabolic improvement and the weight loss observed with EOW persisted for up to 3−6 years of follow-up.[13]

A multicenter retrospective study in Italy showed that patients initiating EOW had better adherence compared with those treated with liraglutide, suggesting that lowering the overall number of injections may contribute to improving both adherence and treatment effectiveness.[14] Therefore, to complement clinical trials data and provide information possibly supporting clinicians in the decision-making process, the aim of the present study was to determine the long-term effectiveness and tolerability of EOW treatment in a real-world clinical setting, as well as to identify individual predictors of drug discontinuation.

METHODS

Study Design, Data Source, and Participants

This monocentric retrospective cohort study was based on data routinely registered in an electronic chart system, MyStar Connect (METEDA, San Benedetto del Tronto [AP], Italy), a software specifically developed to support Italian diabetes outpatient clinics in the management and review of patient data.[15] Data use and analysis were approved by the ethics committee at our institution.

All patients (18−80 years of age) with T2DM diagnosed since at least 1 year prior and prescribed exenatide extended-release 2 mg once weekly for the first time between April 2014 and March 2019 were retrospectively included in this study. Patients with a diagnosis of type 1, secondary, or gestational diabetes were excluded (Figure 1).

Data were collected at baseline (data of first EOW prescription) and at follow-up visits, which were set at 6, 12, and 18 months after EOW initiation. At baseline, the following data were collected: age, sex, diabetes duration, body weight, height, body mass index (BMI), waist circumference (WC), HbA_{1c} level, fasting plasma glucose (FPG), systolic and diastolic

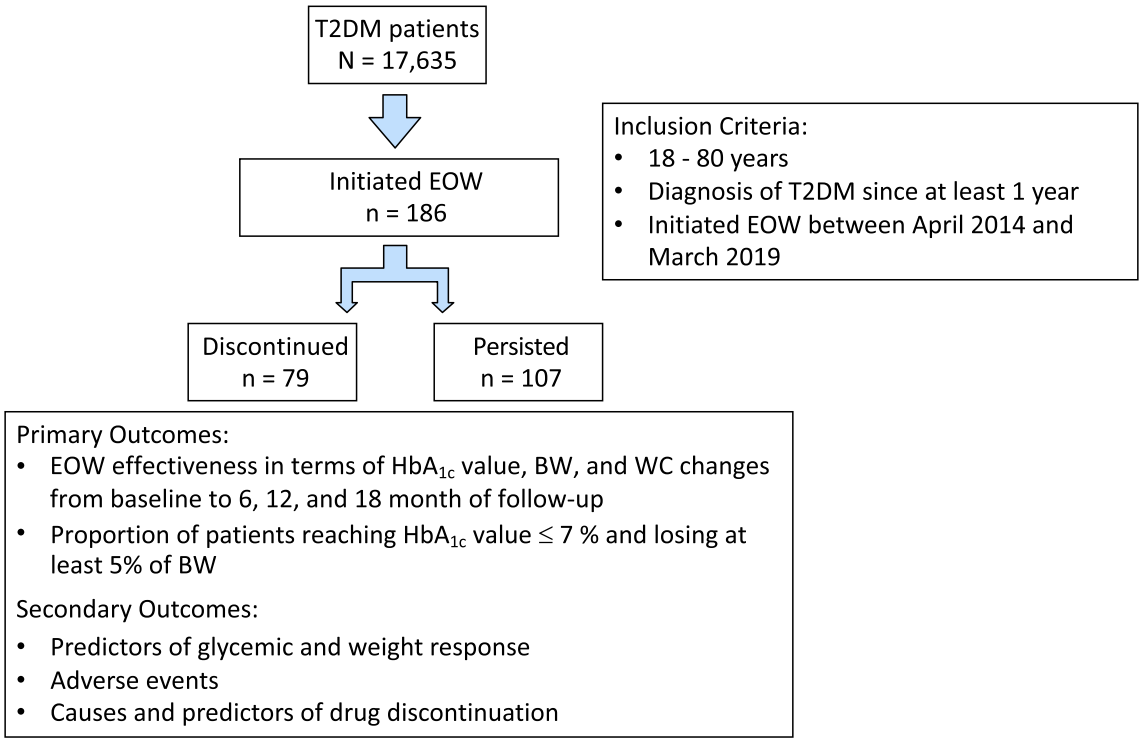

Figure 1. Study flowchart. BW = body weight; EOW = exenatide once weekly; HbA_{1c} = glycosylated hemoglobin; T2DM = type 2 diabetes mellitus; WC = waist circumference.

blood pressures, HDL-C, LDL-C, total cholesterol, triglycerides, serum creatinine, urinary albumin excretion, and background diabetes therapy.

Data on diabetes complications, comorbidities, and concomitant use of lipid-lowering and antihypertensive drugs were also recorded. These data were derived by using physicians' entries in the electronic charts and might have been underreported in some patients. Retinopathy was defined as any stage of diabetic retinopathy, whereas macular edema was reported separately. Peripheral neuropathy diagnosis was based on clinical examination eventually confirmed by electromyography. Nephropathy was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2 and/or the presence of microalbuminuria. Peripheral arterial disease was defined as Leriche-Fontaine stages II to IV and/or the presence of peripheral arterial stenosis documented by Doppler ultrasonography. Stroke or transient ischemic attack was defined as clinically significant neurologic deficits lasting for >24 h (stroke) or <24 h (transient ischemic attack), as reported on the patient's medical record. Ischemic heart disease category included clinical history of myocardial infarction, angina, or relevant coronary stenosis documented by angiography. Left ventricular hypertrophy definition was based on ECG or ultrasound examination. Heart failure classification included New York Heart Association functional classes II to IV diagnosed by a cardiologist. Patients were considered affected by microangiopathy if at least one of the following conditions was present: chronic kidney disease, microalbuminuria, retinopathy or macular edema, or neuropathy. Macroangiopathy was defined as any stenosis ≥50% or any revascularization procedures of coronary, lower limbs, or carotid arteries.

Updated data on HbA_{1c} values, body weight, WC, and antihyperglycemic medications were collected during follow-up visits. Adverse events, causes of withdrawal, and/or switching to another GLP-1RA

were recorded at each visit. Data on costs and pharmacy refill rates were not available.

Outcomes Measures

The primary goal was to investigate: (1) EOW effectiveness in terms of HbA_{1c} values, body weight, and WC changes from baseline to 6, 12, and 18 months of follow-up; and (2) proportion of patients reaching HbA_{1c} values $\leq 7\%$ and losing at least 5% of body weight (variables were considered both separately and as composite end point) at 12 months after EOW treatment.

Secondary outcomes were: predictors of glycemic response, adverse events, causes of treatment withdrawal during the study follow-up, and predictors of early discontinuation.

Statistical Analysis

Continuous variables are expressed as mean and SD, or as median and interquartile range if nonnormally distributed. Categorical data are presented as absolute frequency and percentages.

Longitudinal linear mixed models for repeated measures were applied to assess trends over time in continuous end points (HbA_{1c} values, body weight, and WC). Results are expressed as estimated mean change from baseline with their 95% CIs. Statistical analysis was performed on data available at baseline and 6, 12, and 18 months of follow-up for each patient.

To identify variables associated with glycemic response (HbA_{1c} value $\leq 7\%$ at 12 months), weight changes (body weight loss of 5% at 12 months), and discontinuation during EOW treatment, the χ^2 test and Student's t test (or Mann-Whitney test, if appropriate) were used for categorical and continuous variables, respectively. Statistical significance was defined as $P < 0.05$. Multivariate logistic regression analysis was performed to estimate odds ratios (ORs) for treatment discontinuation (dependent variable) and covariates, including patient characteristics at baseline. Data were analyzed by using SAS software release 9.4 (SAS Institute, Inc, Cary, North Carolina).

RESULTS

Baseline Characteristics

A total of 186 patients (46.2% male) were included in the study. Their baseline demographic and clinical characteristics are shown in Table I. The mean (SD)

Table I. Baseline characteristics of patients treated with exenatide once weekly (EOW) (N = 186). Values are given as mean (SD) unless otherwise indicated.

Characteristic	Value
Age, y	63.2 (8.9)
Male sex	86 (46.2%)
Diabetes duration, y	10.7 (18.3)
Body weight, kg	91 (23)
BMI, kg/m^2	34.2 (6.3)
Waist circumference, cm	111.4 (12.4)
FPG, mg/dL	167.8 (36.1)
HbA_{1c},%	7.8 (0.6)
HbA_{1c}, mmol/mol	62 (7)
Total cholesterol, mg/dL	180.1 (36.1)
HDL-C, mg/dL	47.5 (13.4)
Triglycerides, mg/dL	171.6 (85)
LDL-C, mg/dL	98.6 (29.7)
eGFR, mL/min/1.73m^2	81.2 (18.1)
Creatinine, mg	0.9 (0.2)
*Complications and/or comorbidities**	
Retinopathy	39 of 179 (21.8%)
Macular edema	9 of 179 (5%)
Neuropathy	18 of 176 (10.2%)
Nephropathy	56 of 183 (30.6%)
Peripheral arterial disease	3 of 180 (1.7%)
Stroke or TIA	8 of 184 (4.3%)
Ischemic heart disease	24 of 184 (13%)
Heart failure	12 of 184 (6.5%)
Left ventricular hypertrophy	44 of 157 (28%)
Hypertension	146 of 184 (79.3%)
Dyslipidemia	103 of 184 (56%)
Any microangiopathy	78 of 180 (43.3%)
Any macroangiopathy	31 of 181 (17%)
Background diabetes therapy	
Diet and exercise only	13 (7%)
Oral monotherapy	36 (19.3%)
Oral combined	87 (46.8%)
Oral plus other GLP1-RA	32 (17.2%)
Oral plus basal insulin	18 (9.7%)
Background diabetes therapy by drug class	
Metformin	160 (86%)
Sulfonylurea	36 (19.4%)
Pioglitazone	26 (14%)
DPP-4 inhibitors	59 (31.7%)
SGLT2 inhibitors	16 (8.6%)

Table I. (*Continued*)

Characteristic	Value
Other GLP1-RAs	32 (17.2%)
Basal insulin	18 (9.6%)
Lipid-lowering drugs	
Statin	87 (46.8%)
Ezetimibe	21 (11.3%)
Fibrate	5 (2.7%)
Omega-3 fatty acids	9 (4.8%)
Antihypertensive drugs	
ACE inhibitor or ARB	122 (65.6%)
Alpha$_1$-blockers	5 (2.7%)
Beta-blockers	49 (26.3%)
Calcium channel blockers	40 (21.5%)
Diuretics	62 (33.3%)
Other drugs	
Antiplatelet agents	78 (41.9%)
Anticoagulant agents	6 (3.2%)
Antihyperuricemic agents	29 (15.6%)

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; BMI = body mass index; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; GLP1-RAs = glucagon-like peptide-1 receptor agonists; HbA_{1c} = glycosylated hemoglobin; SGLT2 = sodium-glucose cotransporter-2; TIA = transient ischemic attack.
* No./total no. (%).

age and duration of diabetes were 63.2 (8.9) years and 10.7 (18.3) years, respectively. The majority of patients (75%) were obese, with a mean BMI of 34.2 (6.3) kg/m^2. The mean baseline HbA_{1c} and FPG levels were 7.8% (0.6%) (or 62 [7] mmol/mol) and 167.8 (36.1) mg/dL. The mean estimated glomerular filtration rate was 81.2 (18.1) mL/min/1.73 m^2.

Before EOW prescription, 87 (46.8%) patients had been treated with different oral antidiabetic drug (OAD) combinations (64 with double therapies and 23 with triple therapies), 32 (17.2%) with OADs plus GLP-1RA, and <10% with OADs plus basal insulin. According to drug class, 86% of patients were on metformin, 31.7% on dipeptidyl peptidase-4 inhibitors, 19.4% on sulfonylurea, and <15% on pioglitazone or sodium-glucose cotransporter-2 inhibitors. Comorbidities and diabetes-related complications are shown in Table I.

Glycemic and Weight Control

HbA_{1c} values significantly declined from baseline by −0.9% (95% CI, −1.1 to −0.8; $P < 0.001$) at 6 months, by −0.9% (95% CI, −1.1 to −0.7; $P < 0.001$) at 12 months, and by −0.7% (95% CI, −0.9 to −0.6; $P < 0.001$) at 18 months (Figure 2A). Similarly, FPG showed a decline of −34.2 mg/dL (95% CI, −45.6 to 22.7; $P < 0.001$) at 6 months, which persisted at 12 months (−30.4 mg/dL; 95% CI, −42 to 18; $P < 0.001$) and 18 months (−18.6 mg/dL; 95% CI, −36.7 to 2.6; $P < 0.024$; data not shown) of follow-up.

The mean reduction in body weight from baseline was −2.8 kg at 6 months (95% CI, −3.4 to −2.2; $P < 0.001$), −3.1 kg at 12 months (95% CI, −3.8 to −2.4; $P < 0.001$), and −2.6 kg at 18 months (95% CI, −3.3 to −1.9; $P < 0.001$) of follow-up (Figure 2B).

The proportion of patients achieving the HbA_{1c} target of ≤7% was 61% (87 of 143) after 12 months of EOW treatment (Figure 3A). Compared with patients who did not exhibit a good glycemic response, patients achieving the HbA_{1c} target of ≤7% had shorter diabetes duration (9.5 vs 11.6 years; $P < 0.05$) and lower rates of metformin (80.5% vs 94.6%; $P < 0.05$) or pioglitazone (8% vs 23%; $P < 0.05$) use. Age, sex, baseline HbA_{1c} value, and BMI did not affect response to treatment (data not shown).

Thirty-four percent of patients achieved a 5% weight loss after 12 months of EOW treatment (45 of 134) (Figure 3B). This target was mostly achieved by patients who were GLP-1RA–naive (4.3% vs 27.3%; $P < 0.001$) and were taking a lower dose of metformin (1649 [674] mg vs 1948 [683] mg; $P < 0.05$). Age, sex, diabetes duration, baseline HbA_{1c} value, and BMI did not affect weight response to treatment (data not shown). The proportion of patients achieving the composite end point of both HbA_{1c} target ≤7% and weight loss ≥5.0% was 25.4% (Figure 3C).

We found that among the different drug combinations, patients on EOW plus sulfonylureas, with or without metformin, had a lower achievement rate of the composite outcome compared with patients who were not taking sulfonylureas (2.9% vs 24.2%; $P < 0.05$).

Adverse Events and Discontinuation

Adverse events were reported in 16% of patients (30 of 186). The most common adverse events were gastrointestinal side effects (7.5%) and injection site

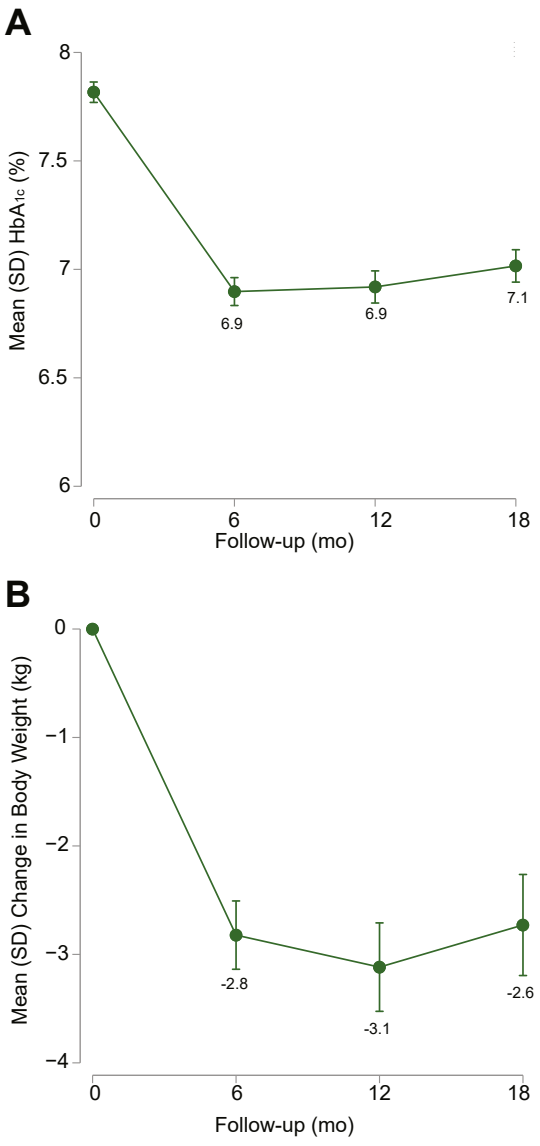

Figure 2. Measures of exenatide once weekly effectiveness during the follow-up period. (A) Longitudinal changes in glycosylated hemoglobin (HbA_{1c}). (B) Mean change in body weight. Data are represented as mean (SD).

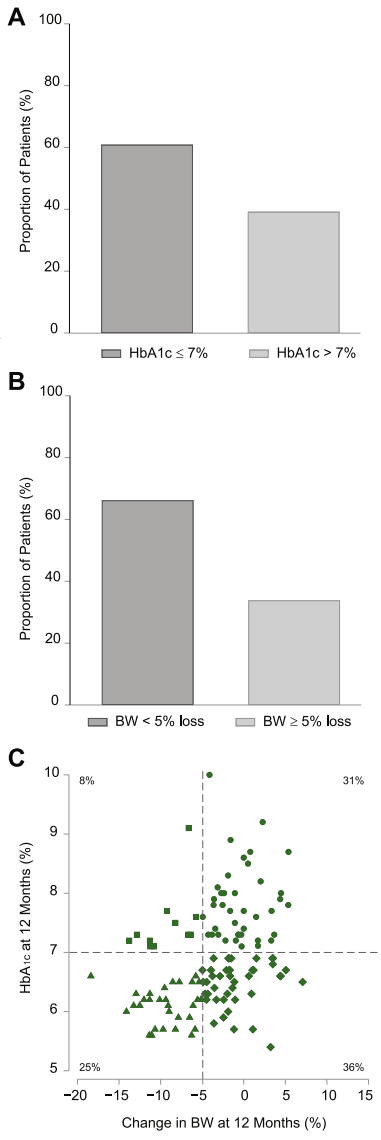

Figure 3. Proportion of patients who achieved at 12 months of follow-up. (A) Glycosylated hemoglobin (HbA_{1c}) target $\leq$7%. (B) Body weight (BW) loss $\geq$5%. (C) The composite endpoint of $HbA_{1c} \leq$ 7% and BW loss $\geq$5%.

reactions such as subcutaneous nodules (6.4%), followed by headache (1.1%) and allergic reactions (1.1%) (Table II). No hypoglycemic events were reported.

A total of 107 patients (57.5%) persisted on EOW. Over the entire follow-up period, 79 patients (42.5%) discontinued treatment (Table III), 30 of whom switched to a different GLP-1RA. The main reasons for discontinuation were limited effectiveness on HbA_{1c} values and/or weight reduction (19.9%), side effects (16.1%), and patient decision (6.5%) (Table II).

Table II. Reasons and time for treatment discontinuation in patients treated with exenatide once weekly (N = 186).

Reasons for Discontinuation	No. (%) of Patients	*Median (IQR)* Time to Discontinuation, d
Low effectiveness	37 (19.9)	438 (207–552)
Adverse events	30 (16.1)	183 (63–309)
Gastrointestinal side effects	14 (7.5)	180 (63–273)
Injection site reactions	12 (6.4)	195 (156–435)
Headache	2 (1.1)	33 (33–33)
Allergic reactions	2 (1.1)	230 (15–444)
Patient decision	12 (6.5)	300 (206–407)
All	79 (42.5)	288 (174–477)

IQR = interquartile range.

Table III. Comparison of patients who persisted on exenatide once weekly treatment versus those who discontinued. Values are given as mean (SD) unless otherwise indicated.

Variable	*Persisted* (n = *107*)	*Discontinued* (n = *79*)	P
Age, y	63.4 (8.3)	63.0 (9.7)	0.999
Sex male, No. (%)	47 (43.9%)	39 (49.4%)	0.462
Diabetes duration, y	10.2 (6.7)	11.3 (7.7)	0.432
Body weight, kg	91.7 (18.9)	90.1 (17.7)	0.667
BMI, kg/m^2	34.5 (6.6)	33.6 (5.9)	0.455
Waist circumference, cm	112.4 (11.9)	109.8 (13.2)	0.123
FPG, mg/dL	167.1 (35.4)	168.8 (37.7)	0.963
HbA_{1c}, %	7.7 (0.7)	7.9 (0.6)	**0.009**
Total cholesterol, mg/dL	176.1 (35.5)	186.5 (36.5)	0.249
HDL-C, mg/dL	47.6 (14.9)	47.2 (11.1)	0.955
Triglycerides, mg/dL	170.6 (76.8)	173.2 (97.7)	0.601
LDL-C, mg/dL	105.7 (33.7)	94.1 (26)	0.059
eGFR, mg/min/1.73 m^2	82.0 (17.3)	79.9 (19.8)	0.869
Creatinine, mg	0.9 (0.2)	0.9 (0.3)	0.380
Background diabetes therapy by drug class			
Metformin	92 (85.6%)	68 (86.1%)	0.580
Sulfonylurea	21 (19.6%)	15 (19%)	0.534
Pioglitazone	15 (14%)	11 (13.9%)	0.580
DPP-4 inhibitors	33 (30.8%)	26 (32.9%)	0.443
SGLT2 inhibitors	11 (10.3%)	5 (6.3%)	0.249
Other GLP1-RAs	20 (18.7%)	12 (15.2%)	0.336
Basal insulin	6 (5.6%)	12 (15.2%)	**0.027**

BMI = body mass index; DPP-4 = dipeptidyl peptidase-4; FPG = fasting plasma glucose; eGFR = estimated glomerular filtration rate; GLP1-RAs = glucagon-like peptide-1 receptor agonists; HbA_{1c} = glycosylated hemoglobin; SGLT2 = sodium-glucose cotransporter-2.
Statistically significant results are in bold.

Overall, the median time (interquartile range) to treatment discontinuation was 288 days (174–477 days). The median time to discontinuation was significantly shorter for "adverse events" than for other reasons, such as limited effectiveness (183 vs 438 days; $P < 0.0001$) or patient decision (183 vs 300 days; $P < 0.05$).

Compared with patients who persisted on treatment, patients who discontinued treatment had higher HbA_{1c} levels at baseline (7.9% vs 7.7%; $P < 0.05$), and a greater percentage of them were on basal insulin (5.6% vs 15.2%; $P < 0.05$) (Table III). Multivariate logistic regression analysis showed that higher HbA_{1c} levels at baseline were an independent risk factor for discontinuation (OR, 1.66; 95% CI, 1.026–2.687; $P < 0.05$) (see the Supplemental Table in the appendix), whereas basal insulin therapy showed a trend toward statistical significance (OR, 2.91; 95% CI, 0.907–9.365; $P = 0.072$).

DISCUSSION

The results of this study indicate that, in a real-world clinical setting, EOW treatment provides sustained and effective glycemic control and induces weight reduction in patients with T2DM over 18 months of follow-up. We found mean reductions in HbA_{1c} and body weight of –0.9% and –2.8 kg after 6 months of EOW initiation, in keeping with findings of other real-world studies investigating EOW effectiveness (the main real-world retrospective studies with 6 months' follow-up are summarized in Table IV).[14,16–20] The observed decrements persisted throughout the 18-month follow-up period in the present study, confirming the long-term effectiveness of EOW.

Our findings are consistent with a post hoc analysis of 3 DURATION extension studies[21–23] showing a mean HbA_{1c} reduction of –1.1% (1.3%) and an average weight loss of 2.4 (5.6) kg in 329 patients continuing on EOW therapy for up to 3 years of follow-up.[24]

The current consensus statement of the American Diabetes Association and of the European Association for the Study of Diabetes recommends an HbA_{1c} target <7% (53 mmol/mol) as a reasonable and desirable goal for many adults with T2DM, with sufficient life expectancy, to obtain microvascular benefits.[25] However, HbA_{1c} targets should be personalized to maximize benefits while limiting the risk of treatment adverse effects such as hypoglycemia and weight gain.[26] Furthermore, a moderate weight loss, defined as a 5%–10% reduction in baseline weight, is needed to improve glycemic control and cardiovascular risk factors, as well as other obesity-related disorders.[27,28] In addition, the same statement considers appropriate GLP-1RA treatment in patients with T2DM with established cardiovascular disease or with the presence of specific indicators of high cardiovascular risk, independently of baseline HbA_{1c} or individualized HbA_{1c} target, to reduce the risk of major adverse cardiovascular events, cardiovascular death, or chronic kidney disease progression.

In the present cohort analysis, the proportions of patients achieving the HbA_{1c} goal of ≤7% and a

Table IV. Mean changes in glycosylated hemoglobin (HbA_{1c}) and body weight at 6 months of follow-up in retrospective real-world evidence studies.

Study	Year	Country	No.	Mean Difference (95% CI) in HbA_{1c}, %	No.	Mean Difference (95% CI) in Body Weight, kg
Saunders et al[16]	2016	US	664	− 0.64 (–0.74 to–0.54)	618	–4.63 (–7.04 to –2.22)
Gorgojo-Martínez et al[17]	2018	Spain	148	–1.10 (–1.39 to –0.81)	148	–3.9 (–4.85 to − 2.95)
Unni et al[18]	2018	US	2133	–0.4 (–0.46 to –0.34)	2133	–1.4 (–1.6 to –1.2)
Fadini et al[14]	2019	Italy	204	–0.7 (–0.85 to –0.55)	204	–2.2 (–2.7 to –1.69)
Morgan et al[19]	2018	UK	244	–1.29 (–1.47 to –1.11)	228	–3.76 (–4.38 to –3.14)
Morieri et al[20]	2020	Italy	198	–0.80 (–1.0 to –0.6)	198	–2.7 (–3.31 to –2.09)

UK = United Kingdom; US = United States.

weight loss ≥5% were 61% and 34%, respectively, after 12 months of EOW treatment (Figure 3). Moreover, 25% of patients attained the ambitious composite end point of both HbA_{1c} value ≤ 7.0% and weight loss ≥5%. In the DURATION-1 extension study, 71% of all patients attained HbA_{1c} values ≤ 7.0% over 1 year of EOW treatment, and most patients (77%) achieved reductions in both HbA_{1c} values and body weight,[29] but the composite end point (both HbA_{1c} value ≤ 7.0% and weight loss ≥5%) was not evaluated. Conversely, in the SUSTAIN 3 (Efficacy and Safety of Once-Weekly Semaglutide Versus Exenatide ER in Subjects With Type 2 Diabetes) trial, comparing the efficacy of semaglutide versus EOW, 40% of EOW-treated subjects achieved HbA_{1c} values ≤ 7.0% at 56 weeks, and 17% of patients had a weight loss response ≥5%.[30] The composite end point of HbA_{1c} reduction ≥1.0% and weight loss ≥5.0% was achieved by 13% of EOW-treated subjects.[30,31] Those discrepancies may be attributed to differences in the studies' design and in the device systems used to administer GLP-1 RA, as asserted by Ahmann et al.[30]

In the present study, we identified shorter duration of diabetes as a predictor of adequate glycemic response, defined as HbA_{1c} values ≤ 7.0% at 12 months. This finding suggests that patients with shorter diabetes duration may benefit from an early initiation of EOW, independently of baseline HbA_{1c} levels.

Some observational studies reported a weaker glycemic response to GLP-1RAs in patients with a longer duration of diabetes.[32–34] Conversely, available data from clinical trials seem to exclude an effect of diabetes duration on the efficacy of GLP1-RAs,[35] likely related to the enrollment of relatively younger subjects with a shorter duration of disease. In the DURATION trials, indeed, the mean diabetes duration was shorter compared with disease duration of patients included in the present real-world study (7 [6] vs 11 [18] years).[36]

Remarkably, in our observations, baseline HbA_{1c} was not a predictor of glycemic response, as suggested by a published meta-analysis regarding the efficacy of GLP-1RAs in patients with T2DM.[35] This discrepancy may be related to the fact that the mean baseline HbA_{1c} value was relatively low in our study population compared with that of the DURATION trials (7.8 [0.6%] vs 8.4 [1.1%]).[36]

Neither baseline body weight nor BMI were predictors of response to EOW treatment, suggesting that EOW treatment is equally effective in obese and overweight patients and in normal weight patients. This is consistent with findings of a post hoc analysis including randomized controlled trial data of 1719 patients, which revealed that EOW treatment was associated with significant improvements in glycemic control and body weight, irrespective of baseline BMI.[37]

EOW treatment was generally well tolerated, with adverse events reported by 16% of patients (Table II). As expected, gastrointestinal side effects (nausea, vomiting, and diarrhea) were the most frequently reported adverse event, followed by injection site reactions, as indicated in randomized controlled trials.[37,38] No hypoglycemic events were reported.

EOW treatment was discontinued in 79 (42.5%) patients throughout the 18-month follow-up period due to limited effectiveness, adverse events, or patient decision, in line with studies based on pharmacy claims data[39,40] and records from the Italian Monitoring Registry on hypoglycemic drugs that revealed a rate of discontinuation for EOW of 45.6% during a 30-month observation period.[41] Conversely, the overall withdrawal rate in the DURATION trials, conducted under rigorously controlled conditions, ranged from 6% to 25%, with 2%–11% of patients discontinuing treatment because of an adverse event, mainly due to gastrointestinal side effects.[13] However, the proportion of patients who withdrew increased over time, reaching 53% after 7 years of EOW treatment.[42]

The median time to treatment discontinuation due to adverse events was 6 months, whereas withdrawals for limited effectiveness and patient decision occurred usually after 1 year of treatment, suggesting that adverse events, especially gastrointestinal, tended to decrease over time, as observed in long-term randomized controlled trials.[13]

EOW represents a good therapeutic option for long-term treatment of T2DM, allowing significant and persistent glycemic control associated with adequate weight loss.[13] Results of its use in a real-world setting in terms of effectiveness and of adherence to therapy are consistent with those observed in controlled clinical trials.

As shown in Table V, according to our results, clinicians should consider that higher HbA_{1c} values at baseline and use of basal insulin are associated

Table V. Summary of factors affecting the response to exenatide once weekly (EOW) treatment. Response to EOW treatment is defined as glycosylated hemoglobin (HbA_{1c}) value $\leq$ 7%, weight loss of at least 5% of baseline body weight, or persistence on EOW treatment.

Response to EOW treatment		
Positively affected by:	Negatively affected by:	Not affected by:
DM duration <10 y	Concomitant therapy with SU	Age and sex
HbA_{1c} value < 7.7%	Baseline therapy with insulin	BMI
	Switch from other GLP1-RAs	

BMI = body mass index; DM = diabetes mellitus; GLP1-RAs = glucagon-like peptide-1 receptor agonists; SU = sulfonylureas.

with a greater risk of discontinuation of EOW, suggesting that delaying therapy until the high HbA_{1c} value is >7.5% (the so called "treat-to-fail" approach or stepwise strategy) might result in suboptimal response to treatment. Among the different possible combination therapies, EOW plus sulfonylureas (with or without metformin) turned out to be the least effective, as a lower rate of patients on this combination achieved the composite outcome of an HbA_{1c} target <7% and a >5% weight loss.

On the other hand, according to our data, patients presenting a better response to EOW treatment have a shorter duration of diabetes (<10 years), have HbA_{1c} values < 7.7% at baseline, are naive to GLP-1RAs treatment, and are treated with low doses of metformin or pioglitazone as background therapy.

The present study had both strengths and limitations. Strengths included: (1) inclusion of nonselected patients initiating EOW in a routine clinical practice setting; (2) evaluation by a clinician of every single electronic chart; and (3) realistic assessment of treatment response and tolerability over a relatively long follow-up period.

We are aware that this study also has several limitations, inherent to its retrospective and observational design. The limitations include: (1) lack of a control group, although our goal was descriptive and not aimed at a head-to-head comparison of the effectiveness GLP-1 RAs; (2) prescription of EOW was based on clinical decisions, with the possibility that some channeling or confounding bias might exist; (3) presence, at follow-up visits, of missing data for some variables (eg, blood pressure, lipid parameters, creatinine and urinary albumin excretion), limiting the possibility to explore the effect of EOW treatment on them; and (4) data are derived by physicians' entries in the electronic charts and might have been underreported in some patients. Finally, we cannot exclude that adverse events were underestimated, especially nonsevere episodes of hypoglycemia, because patients may underreport these to the physicians.

CONCLUSIONS

EOW treatment, in a real-world setting, offers sustained glycemic control and weight reduction over 18 months of follow-up with a satisfactory tolerability profile. Furthermore, this study identified some predictors of treatment response and discontinuation that may support clinicians in patient characterizations and, thus, in appropriately tailoring T2DM therapy to the individual.

CONFLICTS OF INTEREST

Dr. Consoli reports grants and personal fees from AstraZeneca, Novo Nordisk, and Eli Lilly; and personal fees from Boehringer Ingelheim, Merck Sharp & Dohme, Sanofi Aventis, Menarini Diagnostics, Roche Diagnostics, and Takeda, outside the submitted work.

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Drs. Di Dalmazi and Coluzzi were responsible for data collection, analysis and interpretation, and figure and manuscript drafting; Dr. Baldassarre was responsible for manuscript drafting and revision; Drs. Febo, Ginestra, Sorbo, and Dell'Aquila performed data collection; Drs. Rossi and Graziano performed data analysis; and Drs. Formoso and Consoli were responsible for study design, results interpretation, and manuscript drafting and revision. All authors reviewed and approved the final version of the manuscript.

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APPENDIX

Supplemental Table 1. Multivariate logistic regression analysis of factors associated with EOW discontinuation

Variables	OR	95% CI	p value
Age, years	0.99	0.958–1.031	0.729
Sex, male	0.95	0.512–1.768	0.873
Baseline HbA1c %	**1.66**	1.026–2.687	**0.039**
Diabetes duration, years	1.22	0.811–1.837	0.341
BMI $\geq$ 30 kg/m^2	0.95	0.463–1.933	0.879
Basal insulin therapy	**2.91**	0.907–9.365	**0.072**

Note: EOW, Exenatide once weekly; OR, Odds Ratio; CI, Confidence Interval; BMI, Body mass index.