Diabetes Ther (2020) 11:2677–2690
https://doi.org/10.1007/s13300-020-00929-4

ORIGINAL RESEARCH

ANDREW: A Multicenter, Prospective, Observational Study in Patients with Type 2 Diabetes on Persistent Treatment with Dulaglutide

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Received: July 23, 2020 / Accepted: September 11, 2020 / Published online: September 24, 2020

ABSTRACT

Introduction: Dulaglutide, a long-acting glucagon-like peptide-1 receptor agonist (GLP-1RA), became available in Italy in April 2016. The aim of ANDREW (*A*ctive *N*otes on *D*ulaglutide in the *RE*al *W*orld), a multicenter, prospective, observational study, was to evaluate glycemic control and weight (co-primary outcomes) for up to 24 months in the real-life setting in consecutive outpatients with type 2 diabetes (T2D) who initiated dulaglutide. Co-secondary outcomes were durability of treatment effects on both glycated hemoglobin (HbA1c) and body weight.

Methods: Overall, 1584 subjects (696 women, 888 men) with T2D (mean age [± standard deviation] 61.7 ± 10.2 years; mean T2D duration 9.9 ± 6.9 years) were treated with dulaglutide (0.75 or 1.5 mg once weekly) between April 2016 and December 2019.

Results: A total of 1130 patients completed 12 months of follow-up, while 170 patients interrupted treatment before the 12-month endpoint. At 12 months, average HbA1c and average fasting plasma glucose (FPG) were significantly lower compared to baseline levels (− 10 mmol/mol and − 24.9 mg/dL, respectively), as were body weight (− 3.4 kg) and waist circumference (− 3.3 cm) values (all $p < 0.0001$). Among subjects that completed 24 months of follow-up ($n = 270$), the rapid decline in HbA1c and FPG values in the first 12 months was followed by stabilization in the following 12 months (p value for 12–24 months trend: 0.4 and 0.6, respectively).

Conclusions: Dulaglutide is an effective drug for the treatment of T2D that is administered once weekly using a simple auto-injector device. Real-life data confirm the observations in randomized controlled trials that persistent treatment with dulaglutide may help patients with T2D achieve an improvement in some metabolic features and in body weight. It is important that the benefits of therapy with dulaglutide, i.e., the effects of the "glycemic"

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A complete list of the diabetes centers and clinical investigators participating in the ANDREW study is provided in the Acknowledgement section.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s13300-020-00929-4) contains supplementary material, which is available to authorized users.

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and the so-called "extra-glycemic" actions of GLP-1RAs, are supported by diabetes care teams emphasizing the need for patients to maintain a healthy lifestyle.

Keywords: Dulaglutide; Glycemic control; Body weight; Real-life study

Key Summary Points

Why carry out this study?

Dulaglutide, (a long-acting glucagon-like peptide-1 receptor agonist (GLP-1RA), has been studied in several RCTs, but the results may not be applicable to the general diabetes population.

The aims of the multicenter, prospective, observational study ANDREW (*A*ctive *N*otes on *D*ulaglutide in the *RE*al World) were to evaluate the effect of dulaglutide on glycemic control and body weight (BW) and the durability of the benefits of dulaglutide on both glycated hemoglobin (HbA1c) and BW in the real-life setting in outpatients with type 2 diabetes (T2D) with or without risk factors for atherosclerotic cardiovascular disease (ASCVD) or established ASCVD

What was learned from the study?

In the 1130 patients who completed 12 months of follow-up, average HbA1c and fasting plasma glucose (FPG) levels were significantly lower at 12 months than at baseline ((− 10 mmol/mol and − 24.9 mg/dL, respectively), as was BW (− 3.4 kg) (all p value < 0.0001).

Among those who completed 24 months of treatment (N = 270), HbA1c and FGP values had stabilized at 24 months while, conversely, BW continued to decline.

The group with both high baseline HbA1c and BW had the largest HbA1c reduction during the follow-up period (p value < 0.0001).

Real-life data are in agreement with observations in RCTs that persistent treatment with dulaglutide may help patients with T2D to achieve an improvement in some metabolic and anthropometric features.

DIGITAL FEATURES

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INTRODUCTION

Dulaglutide is a long-acting glucagon-like peptide1-receptor agonist (GLP-1RA) that is injected subcutaneously once weekly in patients with type 2 diabetes (T2D) whose blood sugar level is not well controlled with standard treatments [1]. The peakless pharmacological profile of dulaglutide allows an effective metabolic activity between two injections, with steady-state reached after the second week of therapy [1]. Dulaglutide became available in Italy in April 2016 with an AIFA (Italian Medicine Agency) limitation as "add-on" to either metformin, sulphonylureas (SUs), pioglitazone or basal insulin, or in addition to metformin + SUs or metformin + pioglitazone or metformin + basal insulin. The association of dulaglutide + sodium-glucose cotransporter 2 inhibitors (SGLT2-i) is not yet approved for reimbursement by the Italian National Health System. Together with the above-mentioned pharmacological associations (and in other settings), dulaglutide has been studied in a large number of patients with T2D in several randomized clinical trials (RCTs) with a duration of observation ranging from 26 to 102 weeks, including the AWARD (Assessment of Weekly AdministRation of dulaglutide in Diabetes) program [2–8]. The outcomes of the AWARD 1 (dulaglutide added onto pioglitazone and

metformin vs. exenatide) [2], AWARD 5 (dulaglutide vs. sitagliptin) [6] and AWARD 6 (dulaglutide vs. liraglutide in metformin-treated patients) [7] trials formed the basis for the approval of dulaglutide in the USA and Europe. The reduction in glycated hemoglobin (HbA1c) in patients on dulaglutide ranged from 0.87 to 1.51% in the AWARD studies, and the decrease in body weight ranged between 0.87 and 3.03 kg. The findings of the AWARD 9 study [9] resulted in dulaglutide becoming a prescription drug in association with basal insulin. It is important to point out that symptomatic hypoglycemia is more frequent in patients with T2D if dulaglutide is prescribed together with SUs (with or without metformin) or with prandial insulin (prescription not refunded in Italy) [10]. In 2015, the National Institute for Health and Care Excellence (NICE) of the UK published a monograph on this drug, concluding that dulaglutide can be a valid alternative as a second-line treatment of patients with T2D, but not listing it at that time among its guidelines [11]. In 2019, the results of the REWIND (Researching Cardiovascular Events with a Weekly Incretin in Diabetes) study [12] were published. After a 5.4-year median follow-up, the composite primary outcome (non-fatal myocardial infarction, non-fatal stroke, cardiovascular [CV] death, i.e. the classical 3-point MACE [major adverse cardiovascular events]) was lower in those treated with dulaglutide versus those treated with standard therapy ($p = 0.026$) and, moreover, dulaglutide demonstrated beneficial effects on markers of chronic kidney disease (CKD) [12]. In the American Diabetes Association (ADA) Standards of Medical Care in Diabetes—2020, the drug is considered to be a second-line option (after metformin) in patients at high risk of or with established atherosclerotic CV disease (ASCVD), CKD or heart failure independent of HbA1c level [13]. However, given that RCTs are often performed in selected populations, the results of such trial may not be applicable to the general population. Real-world evidence (RWE) may add to our knowledge of the treatment's effectiveness and outcomes in clinical practice outside of the controlled situation of RCTs.

To fill this gap in current knowledge, we have examined the efficacy of dulaglutide on glycemic control and body weight evolution in real-world settings by collecting and analyzing data from 16 diabetes centers located in Lombardy region which share a database with the aim to assess this novel once-weekly GLP-1RA based on practical experience. We have also investigated the degree to which dulaglutide was able to maintain long-lasting metabolic activity (durability) both on metabolic parameters and body weight. This prospective observational study, ANDREW (*A*ctive *N*otes on *D*ulaglutide in the *RE*al *W*orld), was reported according to STROBE guidelines (Electronic Supplementary Material [ESM] Table S1).

METHODS

Aims of the Study

The aims of the multicenter, prospective, observational study ANDREW were to evaluate (1) the effect of dulaglutide on glycemic control (HbA1c and fasting plasma glucose [FPG]) and body weight—co-primary outcomes) and (2) the durability of dulaglutide, i.e. the maintenance of treatment effects both on HbA1c and body weight changes over the whole study period (co-secondary outcomes), in the "real-life" setting of outpatients with T2D, with or without risk factors for ASCVD or established ASCVD, attending the participating diabetes centers.

Participants and Procedures

From April 2016 up to June 2019, 1584 consecutive subjects with T2D attending any of 16 diabetes centers of the Lombardy region of Italy were treated with dulaglutide (0.75 or 1.5 mg once weekly), the prescription of which is limited to diabetes clinics under the AIFA indication (initially in patients with HbA1c ranging from 7.0 to 8.5%; currently, regardless of HbA1c limits, in subjects with previous CV disease or patients at very high risk of CV disease). Among these subjects, 1432 (90.4%) were GLP-1RA naïve, 152 (9.5%) had switched from another

GLP-1RA (exenatide, lixisenatide or liraglutide) and 304 (19.2%) were being treated with a dipeptidyl-peptidase 4 (DPP4) inhibitor (with DPP4 inhibitor treatment suspended when dulaglutide was initiated). Of these 1584 eligible subjects, complete data on age, T2D duration, HbA1c and body weight were available for 1563 patients at the enrollment visit, and these 1564 patients were retained in the analyses; their clinical characteristics are summarized in Table 1. Data on anthropometric features and laboratory tests were collected at baseline and every 6 months thereafter. Patients with type 1 diabetes, cancer or a recent CV event were excluded, as were potential child-bearing women if not taking anti-contraceptive measures, subjects with a history of non-traumatic bone fractures (because of potential exposure to pioglitazone), psychiatric patients or people with GLP-1RA intolerance.

Every patient included in this study, likewise every patient with T2D evaluated in our outpatient clinics, was enrolled in a routine educational program aimed at teaching the patient to follow the correct medical nutrition treatment (MNT) regimen, with the aim to be able to properly perform dulaglutide once-weekly injections and to collect self-monitoring of blood glucose (SMBG) data.

The Bergamo Ethical Committee approved the study (reg. No. 2016/0254), and the study was performed following ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all individual participants included in the study.

Table 1 Clinical and demographic features of patients at baseline for all patients enrolled in the study (n = 1563) and for enrolled patients with at least one follow-up visit within the first 12 months from baseline (initiation of treatment with dulaglutide) (n = 1130)

Clinical and demographic features	Enrolled patients		Patients with at least 1 follow-up visit	
	N[a]	Mean (SD)	*N*[a]	Mean (SD)
Age (years)	1563	61.8 (10.1)	1130	62.1 (9.6)
Diabetes duration (years)	1563	9.9 (6.9)	1130	10.2 (7.0)
HbA1c (mmol/mol)	1563	64.4 (9.1)	1130	64.5 (8.5)
FPG (mg/dL)	1531	163.2 (38.5)	1107	162.8 (38.1)
Serum creatinine (mg/dL)	1439	0.9 (0.3)	1033	0.9 (0.3)
Body weight (kg)	1563	93.5 (18.0)	1130	93.4 (18.2)
Body mass index (kg/m^2)	1559	33.6 (5.7)	1126	33.6 (5.7)
Waist circumference (cm)	1137	112.1 (13.4)	802	112.3 (13.3)
Total cholesterol (mg/dL)	1418	175.7 (35.8)	1013	174.9 (36.0)
HDL cholesterol (mg/dL)	1403	47.0 (11.1)	1001	47.1 (11.1)
Triglycerides (mg/dL)	1400	160.2 (80.3)	1000	158.0 (75.2)
Systolic BP (mmHg)	1451	137.1 (16.7)	1022	137.4 (16.9)
Diastolic BP (mmHg)	1451	80.6 (8.4)	1022	80.7 (8.6)

BP blood pressure, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin, *HDL* high-density lipoprotein, *SD* standard deviation,

[a] *N* refers to the number of subjects enrolled in study for whom complete data on age, type 2 diabetes (T2D) duration, HbA1c and body weight were available

Statistical Analysis

In accordance with the study protocol, we performed a sample size evaluation based on the observed time trend in the co-primary endpoint HbA1c from RCTs and on 1000 simulation runs with ten study centers and three drop-out scenarios. These simulations revealed that a minimum sample size of 120 patients would be required to achieve a statistically significant result of a 6-month decrease in HbA1c of 0.8% and a steady trend thereafter under the worse drop-out case and with a power equal to 90%. Of the 1563 study participants for whom complete data on age, T2D duration, HbA1c and body weight were available at the enrollment visit, 1130 had already completed at least one follow-up visit before 12 months and were included into the longitudinal analyses of this study. Of these 1563 study participants, 778 completed both outpatients visits at 6 and 12 months, while 272 completed only one visit. For the main analyses, we did not input missing information; sensitivity analyses on the subgroup of patients with complete follow-up data (n = 778) are presented in ESM Table S2). The remaining 80 study participants discontinued the treatment within the first 12 months (but with at least one follow-up visit).

For the 1130 study participants for whom all relevant data were available and who had already attended one follow-up visit by 12 months of treatment initiation, we estimated the absolute and the relative 6-month and 12-month change from baseline for the following parameters: HbA1c (mmol/mol), FPG (mg/dL), body weight (kg) and body mass index (BMI, kg/m^2). Data on waist circumference (WC, cm), serum creatinine (mg/dL) and systolic blood pressure (mmHg) are also shown, even if they were not considered to be specific endpoints. We used a repeated-measure linear regression model with age, disease duration, sex and baseline parameter value as covariates, and a random intercept for the study center. The variance–covariance structure was a compound symmetry structure that assumed a constant correlation between repeated visits for each patient. Sensitivity analyses using AR(1) did not alter results substantially. The same approach, but with a log-linear model, was used to estimate relative change, i.e. the ratio between the absolute change and the baseline value. To control for error-I inflation due to multiple testing, in these analyses we consider an alpha level of 0.005 (a 2 time point comparison for 5 parameters; Table 2) to indicate statistical significance, according to Bonferroni's correction. We also estimated 24-month changes in the same parameters on the subsample of 270 patients who completed all four of the scheduled follow-up visits (6, 12, 18 and 24 months), using the same regression approach. These subjects were further categorized into four groups according to baseline levels of HbA1c and body weight, each dichotomized as low or high using the median value as the cutoff. We estimated the 24-month trend in HbA1c and body weight in each group from repeated-measures regression models as described above but with further inclusion of a visit × group interaction term, and tested the null hypothesis of no difference in the slopes across the groups (Wald chi-square test with 12 degrees of freedom). We used SAS version 9.4 statistical software (proc mixed; SAS Institute, Cary, NC, USA) for longitudinal modeling and the R program (R Foundation for Statistical Computing, Vienna, Austria) for drawing figures.

RESULTS

The study enrolled 1584 patients with T2D (696 women, 888 men) who had been started on dulaglutide once weekly. The mean age (± standard deviation) of the patients was 61.7 ± 10.2 years, and the mean duration of T2D was 9.9 ± 6.9 years. Of these 1584 patients, 1130 completed at least one follow-up visit by 12 months after treatment initiation, and 778 completed both visits at 6 and 12 months; a sub-sample of 270 patients completed all four of the scheduled follow-up visits (6, 12, 18 and 24 months). The evolution of the main parameters from baseline to 6 and 12 months after treatment initiation in the 1130 patients with 1-year follow-up data is summarized in Table 2. The parameters of the 778 patients who attended both scheduled visits (6 and 12 months) in

Table 2 Estimated change from baseline in metabolic and anthropometric features at 6 and 12 months after initiation of treatment with dulaglutide

Parameter and time point	Mean	Estimated change from baseline (95% confidence interval)[a]		*p* value[b]
		Absolute	Relative (% of baseline)	
HbA1c (mmol/mol)				
Baseline	64.5	–	–	–
6 months	54.1	− 10.4 (− 11; − 9.8)	− 18.4 (− 19.4; − 17.3)	< .0001
12 months	54.5	− 10.0 (− 10.7; − 9.3)	− 17.8 (− 18.9; − 16.6)	< .0001
FPG (mg/dL)				
Baseline	161.9	–	–	–
6 months	135.1	− 26.8 (− 29.1; − 24.5)	− 17.7 (− 19.2; − 16.2)	< .0001
12 months	137.0	− 24.9 (− 27.5; − 22.4)	− 16.8 (− 18.4; − 15.1)	< .0001
Body weight (kg)				
Baseline	93.6	–	–	–
6 months	90.7	− 2.9 (− 3.2; − 2.6)	− 3.2 (− 3.6; − 2.7)	< .0001
12 months	90.2	− 3.7 (− 4; − 3.4)	− 4.3 (− 4.8; − 3.8)	< .0001
Body mass index (kg/m^2)				
Baseline	33.6	–	–	–
6 months	32.5	− 1.0 (− 1.1; − 0.9)	− 3.2 (− 3.6; − 2.7)	< .0001
12 months	32.2	− 1.3 (− 1.5; − 1.2)	− 4.3 (− 4.8; − 3.7)	< .0001
Waist circumference (cm)				
Baseline	112.3	–	–	–
6 months	109.3	− 3.0 (− 3.7; − 2.2)	− 2.9 (− 3.4; − 2.4)	< .0001
12 months	109.0	− 3.3 (− 4.1; − 2.4)	− 3.0 (− 3.6; − 2.3)	< .0001

Patients with at least 1 follow-up visit were included in the analysis (n = 1130)

[a] From repeated-measure linear model adjusting for age, sex, diabetes duration and baseline value, and a random intercept term for center. The relative change was estimated from log-linear repeated-measure models adjusting for the same covariates and a random intercept term for center

[b] p value for a Wald chi-square test statistic, to test the null hypothesis of no change from baseline (absolute difference)

the first year of treatment are shown in ESM Table S2, and the evolution of the same parameters in 270 patients who completed 24 months of follow-up are shown in Fig. 1 and ESM Table S3.

6- and 12-Month Change

Compared with baseline values, there was a rapid and significant reduction in average HbA1c, FPG, body weight, BMI and WC at the 6-month follow-up after initiation of treatment with dulaglutide once weekly (Table 2). These metabolic improvements were substantially

maintained after 12 months: HbA1c (absolute change − 10 mmol/mol, 95% confidence limit [CI] − 10.7 to − 9.3; relative change − 17.8%, 95% CI − 18.9 to − 16.6), FPG (absolute change − 24.9 mg/dL, 95% CI − 27.5 to − 22.4; relative change − 16.8 mg/dL, 95% CI: − 18.4 to − 15.1), body weight (absolute change − 3.7 kg, 95% CI − 4.0 to − 3.4; relative change − 4.3%; 95% CI: − 4.8 to − 3.8) and WC (absolute change − 3.3 cm, 95% CI: − 4.1 to − 2.4; relative change − 3.0%; 95% CI: − 3.6 to − 2.3) showed a significant evolution (all p value < 0.0001, below the Bonferroni's corrected alpha of 0.005). The results did not change in the subgroup of patients with the complete 12-month follow-up (n = 778; ESM Table S2).

GLP-1RA-Naïve Patients and Those Who Switched from Another GLP-1RA

A specific sub-analysis was performed in patients who were GLP-1RA naïve and in those who had switched from another GLP-1RA who had attended at least one follow-up visit, with the aim to evaluate the clinical response of these two subgroups. A greater response in terms of HbA1c and FPG reduction as well as in the evolution of anthropometric measures was observed in those patients who had been naïve to GLP-1RAs prior to starting dulaglutide once weekly (n = 1004) (ESM Table S4): the HbA1c and FPG levels were − 18.5 and − 17.6% lower, respectively, versus baseline, and body weight and BMI showed a truly satisfying response (− 4.5 and − 3.1%, respectively, vs. baseline) after 12 months. However, patients with any previous treatment with another GLP-1RA (n = 126) (ESM Table S5) also showed a quite satisfying response (HbA1c and FPG: − 12.5 and − 11.4%, respectively, vs. baseline; body weight and BMI − 1.9% both vs. baseline) after 12 months (all p value for testing linear trend < 0.001).

24-Month Change (Figs. 1, 2; ESM Table. S2)

During the first 12 months, we observed (Fig. 1) the same rapid reduction in HbA1c, FPG level and body weight previously described for the entire sample. From 12 months onward, HbA1c (average change between 24 and 12 months + 0.45 mmol/mol, p value for testing linear trend = 0.4) and FPG (− 1.0 mg/dL, p value for testing linear trend = 0.6) were stable. Conversely, body weight continued to decline, but at a reduced pace (average change between 24 and 12 months − 0.5 kg, p value for testing linear trend = 0.04). In the 270 subjects who completed 24 months of follow-up, BMI changed from 33.5 to 32 kg/m^2 (− 1.5; 95% CI − 1.7 to − 1.3) and WC improved from 112.3 to 107.9 cm (− 4.4 cm; 95% CI − 5.2 to − 3.6)

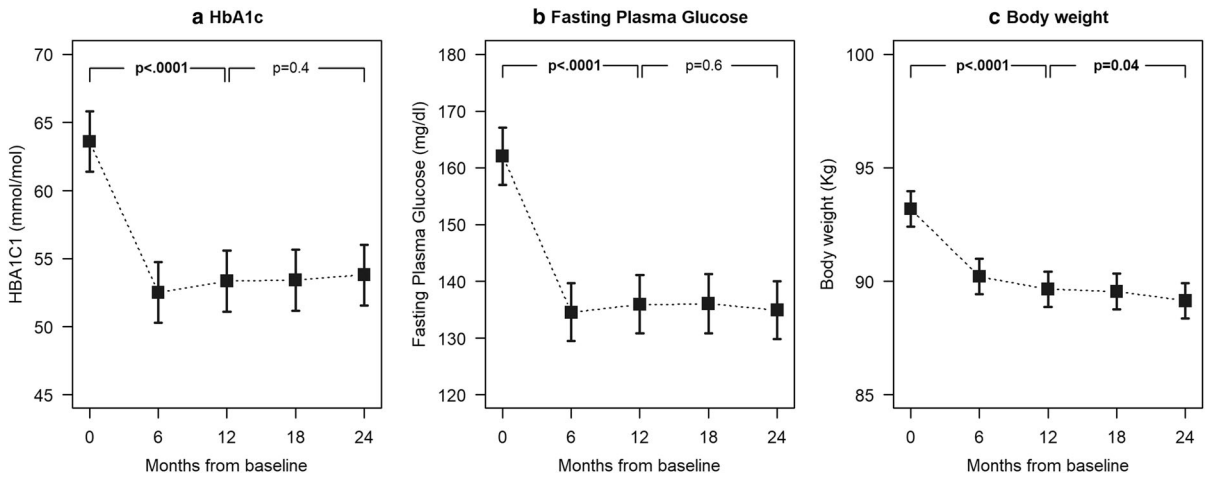

Fig. 1 Evolution of glycated hemoglobin (*HbA1c*) (**a**), fasting plasma glucose (**b**) and body weight (**c**) in 270 patients with type 2 diabetes who completed 24 months of follow-up

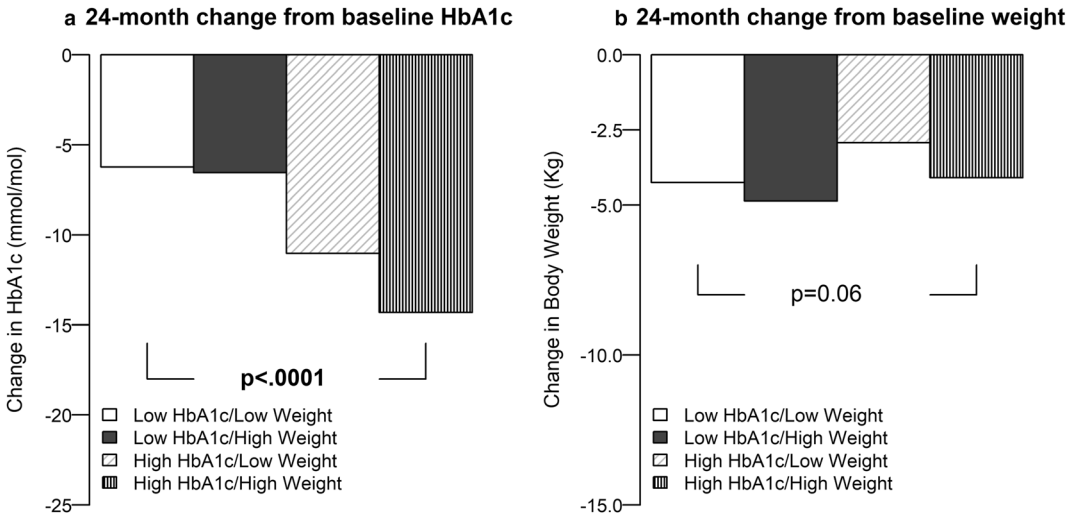

Fig. 2 Change in HbA1c (**a**) and body weight (**b**) in the 270 subjects that completed a 24-month follow-up further classified into four groups according to baseline values of HbA1c and body weight. HbA1c-related p value of the Wald chi-square test for visit × group interaction < 0.0001. Body weight-related p value of the Wald chi-square test for visit × group interaction 0.37. After 24 months, the average reduction from baseline was > 4 kg in three of the four groups, without differences across them ($p = 0.06$; **b**)

(ESM Table S3). In Fig. 2, we show the 24-month change in HbA1c (Fig. 2a) and body weight (Fig. 2b) in the same subjects further classified into four groups according to baseline values of HbA1c and body weight. For HbA1c, the change from baseline was different across the four groups (p value of the Wald chi-square test for visit × group interaction < 0.0001). In particular, at 24 months of follow-up, the group with both high baseline HbA1c and weight had the largest reduction (− 14.3 mmol/mol), almost threefold more than groups with baseline HbA1c below the median ($p < 0.0001$; Fig. 2a). Conversely, we observed no differential time trend in body weight according to baseline levels (p value of the Wald chi-square test for visit × group interaction 0.37). After 24 months, the average reduction from baseline was > 4 kg in three of the four groups, without differences across them ($p = 0.06$; Fig. 2b).

Drug Discontinuation

Use of dulaglutide once weekly was suspended in 170 study participants (14.9%) in the first year of treatment, of whom 90 had no follow-up visit and 80 had attended at least one follow-up visit. Patients who discontinued dulaglutide did not differ from those who continued the therapy in terms of metabolic parameters at baseline (all $p > 0.05$), but they did have worse glycemic control versus those who persisted in the treatment at 12 months from baseline (HbA1c: − 5.50 vs. − 10.30 mmol/mol; $p < 0.001$). Reasons for dulaglutide interruption were related to gastrointestinal side effects (mainly nausea, occasionally diarrhea) and prescription limitation (due to AIFA rules); only a few patients decided not to continue injection therapy for personal reasons.

DISCUSSION

The findings of several RWE trials support the effectiveness of dulaglutide, but to our knowledge only two of these were prospective studies [14, 15], both of which have a number of limitations, such as short duration (3–6 months) and a limited number of cases (< 200). The centers which participated in the present study have some experience in collecting real-life retrospective data [16], and both the European Medicines Agency and the US Food and Drug Administration have approved the use of RWE

to integrate data from RCTs for regulatory decisions [17–19]. We became interested in conducting an independent prospective real-world observational study [15] on the clinical utilization of dulaglutide shortly after it became available clinical use in Italy in 2016, involving 16 different centers in Lombardy region. Our goal was to obtain a picture of the utilization of this novel once-weekly GLP-1RA that is provided with a simple auto-injector to ameliorate compliance.

The authors of a retrospective claims' analysis including 308 adults with T2D [20] reported that dulaglutide was associated with a significant decrease in HbA1c levels, namely a change of 0.9%. A meta-analysis that compared the impact of dulaglutide, exenatide once weekly and liraglutide on HbA1c levels reported an absolute decrease in HbA1c at 6 months of 0.9–1.4% obtained by these GLP1-RAs [21]. Likewise, we observed a reduction in HbA1c in our study population within 6 months of starting dulaglutide once weekly. Our findings in 1130 patients reveal a reduction in HbA1c of nearly 1.0%. Across the AWARD studies [2–8], dulaglutide demonstrated significant improvement of glycemic control irrespective of gender, duration of diabetes or baseline HbA1c, with greater HbA1c and FPG reductions in patients with higher baseline HbA1c. Our results also show a greater reduction in HbA1c in patients who completed 24 months of follow-up (Fig. 2a), with the greatest improvement observed in those with high HbA1c and high body weight at baseline. In a recent pooled analysis [22] of patients treated with dulaglutide, the reductions of HbA1c were similar across gender and among T2D subgroups according to disease duration. Our data showed that the beneficial effect of dulaglutide on glucose control (HbA1c, FPG) after 6 months persisted through the 24 months of dulaglutide therapy. In a retrospective study, Kaneko and colleagues also saw a reduction in HbA1c similar to that in our data after 24 months of dulaglutide treatment both for subjects aged $\leq$ 70 years and those aged $>$ 70 years old (1.3 and 0.7%, respectively) [23]. In REWIND [12], dulaglutide durably reduced HbA1c by a mean absolute amount of 0.6% more than placebo while not increasing hypoglycemia. Our population showed a mean HbA1c relative reduction of 17.8% after 12 months, and of 17.5% after 24 months, albeit starting from a baseline value higher than that reported in the REWIND study. In comparison with REWIND, our patients were younger (61.7 vs. 66.2 years), had a shorter diabetes duration (9.9 vs. 10.5 years) and had a higher BMI (33.6 vs. 32.3 kg/m^2).

In our study dulaglutide therapy was associated with a significant reduction in body weight in the first 6 months of treatment. A really interesting clinical observation was that there was a significant, progressive reduction in body measurements during the study period, with weight, BMI and WC showing a gradual improvement. These observations underline the persistent efficacy of dulaglutide over time. Weight loss is correlated to a reduction in gastrointestinal motility, concomitant with a decrease in appetite and caloric intake, and to the effects of GLP-1RA on the central nervous system [24]. Generally, the duration of diabetes and the baseline HbA1c level did not affect changes in the patients' body weight. Similarly, we found a nearly uniform weight reduction in those who completed the 24-month follow-up regardless of their low or high HbA1c level at baseline, and independently of their low or high weight categorization (Fig. 2b). We noted a decrease in abdominal fat deposition (which correlates with visceral adiposity), as revealed by the progressive evolution of WC: $-$ 3.3 cm after 12 months (Table 2). Such an improvement should bring metabolic benefit to our patients, as WC is positively associated with an increased risk of CV disease [25].

A recent retrospective, multicenter study showed that once-weekly administration of GLP-1 RA therapies may be preferable to once- or twice-daily injections because the reduction in the number of required injections could potentially increase treatment adherence and quality of life [26]. When comparing two injectable GLP-1RAs (dulaglutide and liraglutide) to elicit patients' preferences, dosing frequency and type of delivery system were the most important criteria, emphasizing that when differences in efficacy between medications are small, other treatment features (such as dosing

frequency and delivery system) are of much greater importance to patients [21]. As expected, patients who switched from another GLP-1RA showed a reduction in glucometabolic and anthropometric parameters to a lesser degree than did subjects who were GLP-1RA naïve (ESM Tables 4, 5). These differences can be explained by the initial beneficial effects of the previous GLP-1RA(s) prescribed to the patients, taking into account that the most important reasons to switch to dulaglutide were its once-weekly administration and its auto-injector device.

In terms of treatment persistence, few of our patients stopped using dulaglutide (14.9%) in the first year of treatment. This percentage is lower than that reported in six other RWE studies with a 6- to 12-month duration (26.2–37%) [27]. In one study that compared patients who initiated dulaglutide, albiglutide, exenatide or liraglutide, those on dulaglutide showed a significantly higher adherence to treatment, were more treatment persistent and had lower discontinuation rates compared with those on other GLP-1RAs [28]. In an Italian cohort study, 7319 patients with T2D who initiated exenatide, dulaglutide, liraglutide or lixisenatide were retrospectively identified in a longitudinal prescription database (retail pharmacy data) [29]. Among the investigated treatments, the lowest persistence with therapy was among patients on exenatide twice daily and the highest persistence was among those on dulaglutide once weekly [29].

In our study gastrointestinal adverse events (AEs) were the main cause of discontinuation. We are aware that GLP-1 RAs are associated with gastrointestinal AEs that are related to dose and background medications (especially metformin). However, long-acting agents are known to cause less nausea and vomiting and fewer cases of diarrhea. Bettge and colleagues reported that only a small percentage (< 15%) of patients in their study discontinued dulaglutide treatment in the first year of treatment [30]. According to a very recent observation on Chinese patients with T2D ($N = 787$) who were treated with dulaglutide once weekly in two phase III multicenter trials (AWARD-CHN1 and AWARD-CHN2) [31], most of the gastrointestinal AEs associated with dulaglutide were mild to moderate in severity; their incidence was more pronounced during the first 2 weeks of dulaglutide treatment but declined rapidly as treatment continued. Healthcare providers should take gastrointestinal-related issues into account when prescribing a GLP-1RA, but disparities between patient experiences and physician perceptions have been revealed, suggesting gaps in physician–patient communication [32]. Unfortunately, we did not have data on the prevalence of diabetic autonomic neuropathy in our patients to better evaluate the gastrointestinal effects of dulaglutide. No cases of pancreatic cancer or acute pancreatitis in association with dulaglutide have been recorded in our clinical experience. Taking all these points into consideration, GLP-1RAs are considered to be safe drugs [33, 34].

We highlight here that the healthcare teams participating in the ANDREW study always educated each patient individually regarding MNT, physical activity in their daily living, and the correct timing of the dulaglutide injection. In a recent observation [35], medication adherence was low in a real-world population, particularly for GLP-1RAs, although such patients displayed the strongest weight loss benefit. The recent ADA Standard of Care [13] recommends selecting drug therapies that have a weight loss or weight-neutral effect for the management of T2D; consequently, overweight and obese patients should be encouraged to enhance their adherence to treatment in order to benefit the most from therapies that are associated with weight loss.

Lastly, the authors of a very recent pragmatic literature review [27] of 29 studies have summarized RWE for dulaglutide, suggesting that this once-weekly GLP-1RA may be associated with a clinically relevant decrease in HbA1c and a favorable therapeutic profile in routine clinical practice regarding adherence, persistence and discontinuation rates.

Limitations of the Study

A major limitation of our present study is the lack of a control group as well as the lack of data

on microvascular complications and the occurrence of hypoglycemic episodes. However, ANDREW is an independent study and represents a remarkable organizational effort by healthcare centers in our region. Many meetings, webinars and conventions were arranged with the aim to share aims and data collection on clinical outcome evaluation. The diabetes care teams involved in the study (endocrinologists, internists, nurses, nutritionists, psychologists) carried out their normal daily activities, according to international and national guidelines: effective behavior management and psychological well-being should always be emphasized with any pharmacologic therapy [36]. Recording data on the utilization of dulaglutide was an agreed-upon strategy to better understand which benefit could be valuable for our patients with T2D when prescribed a long-acting GLP-1RA injectable through a simple auto-injector device. Unfortunately, there were many missing data points in our database, both during the first year of observation but particularly during the long period. We hope to improve the precision of our data collection in the future, but fear that there will be a progressive reduction in the full completion of this large clinical study during duration of the study. Moreover, 152 patients (among 1584: 9.59%) switched to dulaglutide from another GLP-RA, and it is possible that GLP-1RA-naïve subjects will have greater benefit from the treatment than patients who switch from another drug in the same class. However, dulaglutide-naïve patients should have presented more gastrointestinal AEs than subjects who switched from another injectable incretin. A potential bias of our study is that the changes in the diabetes treatment after the initiation of dulaglutide, such as the discontinuation of SUs and the titration of insulin, could have influenced the results. These are some of the risks of a "real-world" prospective trial, performed without any grant, with no data managers, but with the best will to recommend the optimal care for our patients.

CONCLUSION

Dulaglutide is an effective drug that is provided with a simple auto-injector device that requires one single administration per week. Real-life data confirm observations in RCTs that persistent treatment with dulaglutide may help patients with T2D achieve an improvement in both a number of metabolic features and body weight due to the metabolic activity of the drug (both "glycemic" and the so-called "extra-glycemic" action of GLP-1RAs). However, the diabetes care team needs to maintain a continuous education program for patients on the need to maintain a proper lifestyle.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge all of the nurses and nutritionists involved in the study, as well as the colleagues and other healthcare professionals of the Diabetes Regional Centers participating in the study. Special thanks to Ms Arianna Bossi for the professional proof-reading of the manuscript.

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Funding. No funding or sponsorship was received for this study or publication of this article. The Rapid Service Fee was funded by the authors.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published

Author Contributions. ACB, GL designed the study; ACB, GL, VDM, CS coordinated data collection; GV performed statistical analyses; ACB, GL and GV wrote the manuscript; VDM, CS edited the text; all the Authors revised the paper for the final submission.

Disclosures. Antonio C Bossi received research grants from Lilly SpA, Novo Nordisk SpA, Sanofi SpA, MSD Italia SpA, Astra Zeneca SpA, Johnson & Johnson SpA, Boehringer Ingelheim SpA, Takeda SpA, Pikdare SpA, Bayer SA outside the submitted work. Valentina De Mori has nothing to disclose. Cristiana Scaranna received research grants from Lilly SpA, Novo Nordisk SpA, Sanofi SpA and Astra Zeneca SpA outside the submitted work. Giovanni Veronesi received sponsorship from Fenix SpA for the statistical analyses. Giuseppe Lepore received research grants from Lilly Spa, Novo Nordisk SpA, Sanofi SpA, Astra Zeneca SpA, MSD Italia SpA and Abbott Diabetes Care outside the submitted work.

Compliance with Ethics Guidelines. The Bergamo Ethical Committee approved the study (reg. N. 2016/0254) which was performed following the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all individual participants included in the study.

Prior Presentation. Preliminary data were presented at the 27th National Meeting of the Italian Diabetes Association and at the 25th Lombardy Meeting of the Italian Diabetes Association.

Data Availability. Individual participant data will be shared in datasets in an anonymized format. The data will be available one year after research completion upon reasonable request.

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