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Long-Term Effectiveness of Liraglutide for Treatment of Type 2 Diabetes in a Real-Life Setting: A 24-Month, Multicenter, Non-interventional, Retrospective Study

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ABSTRACT

Introduction: The aim of the study was to evaluate whether the reduction in glycated hemoglobin (HbA1c) observed in clinical trials with liraglutide in type 2 diabetes (T2D) could be attained in routine clinical practice.

Methods: ReaL was a multicenter, non-interventional, observational, retrospective, longitudinal study on the effectiveness of liraglutide, a human glucagon-like peptide-1 analog, in individuals with T2D treated in daily practice in Italy. Between 26 March and 16 November 2015, data were taken from clinical records of patients aged ≥ 18 years with treatment follow-up data of up to 24 months and who received their first prescription of liraglutide in 2011.

Results: A total of 1723 patients were included in the analysis. At baseline, mean age was 58.9 years, duration of diabetes was 9.6 years, and HbA1c was 8.3%. At 12 months, 36.1% of patients were prescribed the maximum 1.8 mg dose; 43.5% [95% confidence interval (CI): 40.9;

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46.2] of patients attained the primary outcome of a reduction in HbA1c of $\geq 1\%$ point at 12 months. At 24 months, 40.9% (95% CI 38.1; 43.7) of patients had attained the HbA1c target of $\leq 7\%$. Additionally, body weight significantly decreased by 3.4 kg (95% CI $-$ 3.6; $-$ 3.1, $p < 0.0001$).

Conclusion: In this observational study conducted in routine clinical practice for up to 2 years, treatment with liraglutide improved HbA1c and reduced body weight in a similar fashion to that observed under randomized clinical trial conditions. The data support the use of liraglutide as an effective treatment for T2D in clinical practice.

INTRODUCTION

The American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) position statement emphasized the importance of an individualized glycemic target, as well as an individualized approach to diabetes therapy, based on a variety of patient- and disease-specific factors [1, 2]. Particularly, since overweight and hypertension are highly prevalent in individuals with type 2 diabetes (T2D) [3, 4], an optimal diabetes therapy would not only provide improved glycemic control but also address other associated comorbidities of T2D. Glucagon-like peptide-1 (GLP-1) receptor agonists have been shown to improve glycemic control and reduce body weight in individuals with T2D [5]. They are recommended as a second-line therapy when diet, exercise and metformin do not provide adequate glycemic control, or as an add-on treatment with sulfonylureas, thiazolidinedione, sodium-glucose cotransporter 2 inhibitor (SGLT2i) or insulin [6] in circumstances where metformin is contraindicated or not tolerated [7].

The efficacy and safety of liraglutide, a human GLP-1 analog, have been demonstrated in the Liraglutide Effect and Action in Diabetes (LEAD) study program of randomized controlled trials [8–13]. Additionally, the LEADER trial reported cardiovascular benefits with liraglutide when used in individuals with T2D at increased risk of cardiovascular disease [14]. Following the regulatory approval of liraglutide, providing real-world evidence for the effectiveness and safety of liraglutide under routine clinical practice conditions is an important step in ensuring appropriate use of the drug in daily practice and confirming the clinical benefits/risks expected, based on the approved label.

The effectiveness of liraglutide under these conditions has been observed in several European countries, including Italy. However, these studies were limited by either a short follow-up period or suboptimal sample size [15]. Therefore, the overall aim of the ReaL study (NCT02255266) was to retrospectively evaluate the long-term effectiveness of liraglutide in routine clinical practice in Italy. The primary objective of the study was to evaluate whether the reduction in glycated hemoglobin (HbA1c) observed in clinical trials could be attained in patients with T2D routinely managed in outpatient clinics. Secondary objectives included evaluation of the attainment of beneficial effects on body weight, lipid profile, and blood pressure, under the same conditions.

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METHODS

ReaL was a multicenter, non-interventional, observational, retrospective, longitudinal study

on the effectiveness of liraglutide in outpatients with T2D, treated in daily practice in 45 diabetes clinics in Italy. Patients aged ≥ 18 years (as per the Victoza® summary of product characteristics [6]) were eligible if they were diagnosed with T2D and received their first prescription of liraglutide in 2011. No exclusion criteria were set and treatment discontinuation during the 24-month study period did not represent a reason for exclusion.

A total of 1788 patient records were extracted from an electronic clinical record (ECR) system widely used for the routine management of patients with T2D in diabetes centers across Italy between 26 March and 16 November 2015. Data were extracted at first prescription of liraglutide (baseline) and after approximately 4, 12 and 24 months of treatment, as recommended by the Italian Standards of Diabetes Care [16] and reported on web-based case report forms. Patient records were obtained from the ECR system on a consecutive basis to minimize the risk of bias.

The primary endpoint was the proportion of patients with an HbA1c reduction ≥ 1% point after 12 months of treatment. Secondary endpoints included the proportion of patients with an HbA1c reduction ≥ 1% point after 4 and 24 months, proportion of patients with a body weight reduction ≥ 3% and composite endpoint of the two after 4, 12 and 24 months. Additionally, the proportion of patients attaining the ADA/EASD HbA1c target of ≤ 7% after 4, 12 and 24 months was recorded. Continuous secondary endpoints included the change in HbA1c, body weight, blood pressure and lipid profile from baseline to 24 months and the proportion of patients discontinuing treatment for any reason at 4, 12 and 24 months.

Statistical Analysis

Baseline characteristics are presented as mean ± standard deviation (SD). For continuous outcomes, data presented are derived from the intention-to-treat (ITT) population, comprised of all patients who received their first prescription of liraglutide in 2011 irrespective of interruption before 24 months. Data were analyzed with hierarchical linear models to assess trends over time. Within-patient correlations and unequal time points were accounted for, using an unstructured correlation type linear model, and changes from baseline were presented as estimated treatment difference (ETD) and 95% confidence intervals (CI). For categorical endpoints, data were analyzed using a general linear model, post hoc test contrasts were assessed at each time point, and data were expressed as frequencies and percentages with 95% CI. Missing data and the risk of bias from discontinuation of treatment were accounted for by using longitudinal models. All analyses were performed at the 5% level of significance. A sample size estimate of 1574 patients was based on 50% of the subjects maintaining an HbA1c reduction of ≥ 1% point after 12 months. Statistical analyses were performed using SAS v9.4 (SAS Institute, Cary, NC). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients before being included in the study.

RESULTS

Baseline Characteristics and Subject Disposition

The results presented reflect the data available as of 31 December 2015. Overall, 1788 patients were extracted from the ECR system; 65 patients were excluded from the analysis, leaving 1723 patients at baseline (45.1%, female; 54.9%, male). Of the 65 excluded patient records, 56 were omitted owing to the absence of clinical data on the ECR, 6 patients did not give informed consent for the use of their information, and 3 had initiated liraglutide prior to 2011. The numbers of patients with available data at the 4-, 12- and 24-month follow-up were 1499, 1413 and 1217, respectively (Table 1).

Baseline characteristics are presented in Table 2. Mean age was 58.9 years, and mean duration of diabetes was 9.6 years. Mean HbA1c

Table 1 Proportion of patient records with available data at each study visit

Variable	Baseline	4 months	12 months	24 months
Group size (N)	1723	1499	1413	1217
HbA1c (%)	95.4	96.7	97.5	97.7
Fasting plasma glucose (%)	93.1	94.5	94.2	95.0
Weight (%)	95.9	97.0	95.8	95.4
BMI (%)	94.5	95.9	94.8	94.5
Waist circumference (%)	67.1	68.5	70.5	67.2
Systolic blood pressure (%)	81.7	80.7	80.3	80.2
Diastolic blood pressure (%)	81.6	80.8	80.1	80.2
Total cholesterol (%)	72.3	65.5	70.6	73.1
HDL cholesterol (%)	69.8	64.5	69.2	70.8
LDL cholesterol (%)	55.3	51.4	56.3	57.4
Triglycerides (%)	71.4	65.4	69.0	72.6
Albuminuria (%)	31.7	32.3	34.4	35.3
Liraglutide dosage (%)	88.5	90.0	92.0	92.4

BMI body mass index, *HbA1c* glycated hemoglobin, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein

at baseline was 8.3%, and mean fasting plasma glucose (FPG) was 171.8 mg/dl. Mean baseline body mass index (BMI), weight and waist circumference were 35.6 kg/m^2, 99.6 kg and 115.5 cm, respectively. Mean estimated glomerular filtration rate at baseline was 85.0 ml/min/1.73 m^2. Data for diabetic complications showed that 13.1% and 1.9% of patients presented with a personal history of coronary heart disease and stroke, respectively. Peripheral vascular disease was present in 6.7% of patients, while diabetic retinopathy and sensory motor neuropathy were present in 18.5% and 13.5% of patients, respectively.

Liraglutide Administration

The highest dose of liraglutide (1.8 mg) was not systematically prescribed in the clinical setting. At baseline, 26.4% of patients were prescribed a daily dose of 0.6 mg, 68.3% prescribed 1.2 mg and 5.3% prescribed 1.8 mg. At 12 months, prescription of 0.6 mg, 1.2 mg and 1.8 mg was

5.4%, 58.5% and 36.1%, respectively. Regarding concomitant use with other anti-diabetic medication, at baseline, 46.6% of patients used liraglutide in combination with metformin, 26.5% with metformin and sulfonylurea, and 5.8% with basal insulin. In terms of treatment modality, liraglutide was used as an adjunct treatment in 63.2% of patients, as a switch from a previous drug in 33.4% and in the context of a reduction in the total number of glucose-lowering drugs in 3.4% of patients.

Primary and Secondary Outcomes

During the study, 43.5% (95% CI 40.9; 46.2) of patients attained a reduction in HbA1c of $\geq 1\%$ point at 12 months (Table 3). After 4 months, 44.3% (95% CI 41.8; 47.0) of patients had a reduction in HbA1c of $\geq 1\%$ point, 49.6% (95% CI 47.0; 52.2) of patients attained a reduction in body weight of $\geq 3\%$, and 26.0% (95% CI 23.7; 28.4) attained the composite endpoint of both targets. At 24 months, the proportions of

Table 2 Baseline characteristics

Variable	Sub-variable	Mean ± SD or %
Patients (N)		1723
Age (years)		58.9 ± 9.5
Sex (%)	Females	45.1
	Males	54.9
Diabetes duration (years)		9.6 ± 7.1
Categorical diabetes duration (%)	< 5 years	32.2
	5–10 years	30.7
	> 10 years	37.1
Diabetes complications		
Coronary heart disease (%)		13.1
Stroke (%)		1.9
Peripheral vascular disease (%)		6.7
Diabetic retinopathy (%)		18.5
Sensory-motor neuropathy (%)		13.5
Dyslipidemia (%)		65.6
HbA1c (%)		8.3 ± 1.4
Categorical HbA1c (%)	≤ 7.5	30
	7.6–8.0	20.6
	8.1–8.9	25.9
	> 9.0	23.4
Fasting plasma glucose (mg/dl)		171.8 ± 52.2
Body weight (kg)		99.6 ± 18.9
BMI (kg/m^2)		35.6 ± 5.9
Categorical BMI (%)	27.1–30 kg/m^2	11.9
	30.1–39.9 kg/m^2	61.9
	≥ 40 kg/m^2	21.4
Waist circumference (cm)		115.5 ± 13.4
Systolic blood pressure (mmHg)		139.3 ± 18.1
Diastolic blood pressure (mmHg)		81.3 ± 10.0
Total cholesterol (mg/dl)		180.8 ± 39.8
HDL cholesterol (mg/dl)		45.0 ± 10.9
LDL cholesterol (mg/dl)		102.9 ± 35.3
Triglycerides (mg/dl)		172.0 ± 90.8

Table 2 continued

Variable	Sub-variable	Mean ± SD or %
Albuminuria (mg/l)		53.2 ± 123.8
eGFR (ml/min/1.73 m^2)		85.0 ± 19.1
Categorical eGFR (%)	$\leq$ 30 ml/min/1.73 m^2	0.1
	> 30–< 60 ml/min/1.73 m^2	11.4
	$\geq$ 60–< 90 ml/min/1.73 m^2	43.1
	$\geq$ 90 ml/min/1.73 m^2	45.4

BMI body mass index, *CKD-EPI* Chronic Kidney Disease Epidemiology Collaboration, *HbA1c* glycated hemoglobin, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *eGFR* estimated glomerular filtration rate (using the CKD-EPI formula)

Table 3 Summary of categorical effectiveness endpoints

Endpoint	4 months		12 months		24 months	
	Frequency	% (95% CI)	Frequency	% (95% CI)	Frequency	% (95% CI)
Patients with HbA1c reduction $\geq$ 1% point	620/1398	44.3 (41.8;47.0)	577/1325	43.5 (40.9;46.2)	472/1136	41.5 (38.7;44.4)
Patients with HbA1c $\leq$ 7%	645/1499	44.5 (42.0;47.1)	611/1413	44.4 (41.8;47.0)	486/1217	40.9 (38.1;43.7)
Patients with weight relative reduction $\geq$ 3%	704/1499	49.6 (47.0;52.2)	686/1413	52.2 (49.5;54.9)	608/1125	54.0 (51.1;56.9)
Composite endpoint (i.e., patients with an HbA1c reduction $\geq$ 1% point and weight relative reduction $\geq$ 3%)	349/1342	26.0 (23.7;28.4)	314/1256	25.0 (22.7;27.5)	274/1073	25.5 (23.0;28.2)

CI confidence interval, *HbA1c* glycated hemoglobin

patients at each endpoint were 41.5% (95% CI 38.7; 44.4), 54.0% (95% CI 51.1; 56.9) and 25.5% (95% CI 23.0; 28.2), respectively. Furthermore, at 24 months, 40.9% (95% CI 38.1; 43.7) of patients had attained the HbA1c target of $\leq$ 7% [16].

Table 4 shows changes in continuous outcomes from baseline to 24 months. At 24 months, mean HbA1c had decreased by 0.8% (95% CI − 0.8; − 0.7, $p < 0.0001$), with a reduction of 0.9 (95% CI − 0.9; − 0.8) at 4 months generally maintained throughout the study (Fig. 1). Mean change in HbA1c from baseline, split by subgroup of concomitant antidiabetic medication, is shown in

Supplementary Figure S1. FPG was reduced by 23.0 mg/dl (95% CI − 25.8; − 20.2, $p < 0.0001$).

Improvements in non-glycemic outcomes were also observed following 24 months of treatment with liraglutide. Body weight decreased significantly by 3.4 kg (95% CI − 3.6; − 3.1) and significant reductions were observed in systolic (SBP) and diastolic blood pressure (DBP) [− 3.9 mmHg (95% CI − 5.1; − 2.8) and − 1.9 mmHg (95% CI − 2.5; − 1.3), respectively, both $p < 0.0001$]. Regarding the lipid profile, total cholesterol (TC) was reduced by 11.1 mg/dl (95% CI − 13.5; − 8.8, $p < 0.0001$), low-density lipoprotein (LDL) cholesterol by 11.2 mg/dl (95% CI − 13.5; − 8.8, $p < 0.0001$) and

Table 4 Changes from baseline to 24 months in continuous outcomes

Variable	Baseline (estimated mean, 95% CI)	4 months (estimated mean change, 95% CI)	12 months (estimated mean change, 95% CI)	24 months (estimated mean change, 95% CI)
HbA1c (%)	8.3 (8.22; 8.34)	− 0.9 (− 0.94; − 0.78)	− 0.8 (− 0.90; − 0.75)	− 0.8 (− 0.84; − 0.72)
Fasting plasma glucose (%)	171.9 (169.5; 174.3)	− 23.7 (− 27.0; − 20.4)	− 24.9 (− 28.0; − 21.8)	− 23.0 (− 25.8; − 20.2)
Body weight (%)	99.5 (98.6; 100.4)	− 2.8 (− 3.2; − 2.4)	− 3.3 (− 3.7; − 3.0)	− 3.4 (− 3.6; − 3.1)
Systolic blood pressure (%)	138.9 (137.9; 140.0)	− 4.0 (− 5.39; − 2.53)	− 4.8 (− 6.14; − 3.44)	− 3.9 (− 5.0; − 2.80)
Diastolic blood pressure (%)	81.2 (80.7; 81.8)	− 0.9 (− 1.57; − 0.14)	− 1.3 (− 2.01; − 0.64)	− 1.9 (− 2.54; − 1.30)
Total cholesterol (%)	180.5 (178.2; 182.8)	− 12.0 (− 15.2; − 8.8)	− 11.0 (− 13.9; − 8.2)	− 11.1 (− 13.5; − 8.8)
HDL cholesterol (%)	44.8 (44.2; 45.4)	− 0.6 (− 1.26; − 0.09)	0.8 (0.23; 1.40)	1.3 (0.85; 1.82)
LDL cholesterol (%)	103.5 (101.5; 105.6)	− 9.0 (− 11.81; − 6.11)	− 9.0 (− 11.64; − 6.41)	− 11.2 (− 13.49; − 8.82)
Triglycerides (%)	172.3 (167.5; 177.2)	− 6.0 (− 12.34; 0.27)	− 12.7 (− 18.35; − 7.00)	− 9.4 (− 14.21; − 4.49)

CI confidence interval, *HbA1c* glycated hemoglobin, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein

triglycerides by 9.4 mg/dl (95% CI − 14.2; − 4.5, $p = 0.0002$). High-density lipoprotein (HDL) cholesterol increased by 1.3 mg/dl (95% CI 0.9; 1.8, $p < 0.0001$). It is important to note that reductions in SBP and LDL cholesterol levels were evident in patients not exposed to anti-hypertensive or lipid-lowering treatment intensification during the study. Changes in continuous outcomes versus baseline at 4, 12 and 24 months, split by prescribed dose, are shown in Supplementary Table S1.

After 24 months, 370 patients (21.5%) had discontinued liraglutide. The most common reason for treatment discontinuation, as reported by 45 patients (2.6%), was 'intolerance' followed by 'gastrointestinal adverse events', reported in 28 patients (1.6%).

DISCUSSION

The ReaL study is the largest observational, non-interventional analysis of liraglutide effectiveness in patients with T2D in Italian clinical practice.
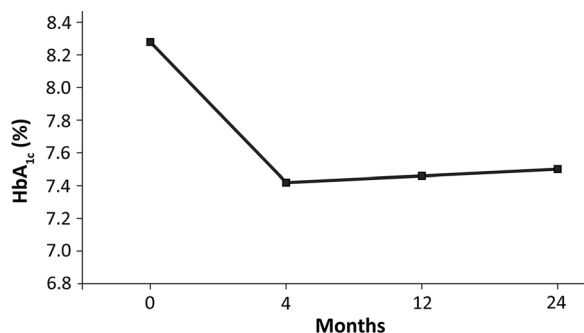
Fig. 1 Mean HbA1c from baseline to 24 months. *HbA1c* glycated hemoglobin

Patient Characteristics

Retrospective, consecutive sampling of patients from clinical practice produced a cohort representative of patients routinely prescribed liraglutide. On initiation of liraglutide, mean HbA1c was 8.3%. Mean diabetes duration was around 10 years, and the proportion of patients initiating liraglutide was generally balanced among categories of diabetes duration. Furthermore, mean duration of diabetes was greater than that reported in the LEAD trials, along with BMI and weight. Mean SBP and DBP was 139.3 and 81.3 mmHg, respectively; however, at baseline, 60% of individuals were classed as hypertensive (SBP 140 mmHg, DBP 90 mmHg). Dyslipidemia was present in 65% of patients prescribed liraglutide at baseline and coronary heart disease present in 13.1% of patients, while 18.5% and 13.5% of patients had been previously diagnosed with diabetic retinopathy and sensory-motor neuropathy, respectively.

Main Findings

Over 40% of patients achieved the primary outcome of a ≥ 1%-point reduction in HbA1c at 12 months, and 40.9% reached the HbA1c target of ≤ 7.0%. Considering the role of attaining and maintaining the HbA1c target in halting the progression of microvascular diseases, this is an important finding. Comparable results have been observed under similar conditions in several European countries, including Italy [17–19].

A statistically significant reduction in HbA1c of 0.9% was observed after 4 months with liraglutide ($p < 0.0001$) and was maintained at both 12 (0.8%) and 24 months (0.8%), demonstrating encouraging durability with liraglutide under real-life conditions. The reduction in HbA1c at 12 months was smaller than that observed over the same period in the ROOTS [20] study. However, this may be the consequence of the higher baseline HbA1c reported in the ROOTS [20] trial. The mean reduction in HbA1c in this study was similar to that reported in the LEAD studies [8–13] despite differences in study design and the beneficial effects of anti-diabetic treatment administered prior to the initiation of liraglutide. Unlike the LEAD trials, in this study approximately one-third of patients were switched to liraglutide from other anti-diabetic drugs, while 3.4% of patients were prescribed liraglutide in lieu of multiple anti-diabetic drugs. This is reflected in the large proportion of patients with an HbA1c ≤ 7.5% at baseline (Table 2). Despite a greater baseline duration of diabetes and BMI in the present study, the HbA1c change profile (with an early decrease followed by the leveling off in HbA1c) was comparable to the LEAD trials (Fig. 1).

At 24 months, the proportion of patients with a ≥ 3% reduction in body weight was 54.0%, with the reduction from baseline being statistically significant. This is consistent with the weight loss observed in the LEAD clinical trials [8–13] and comparable to that reported by other observational trials [20].

Safety and Treatment Discontinuation

The LEADER trial recently confirmed the cardiovascular safety of liraglutide 1.8 mg in individuals with T2D at increased risk of cardiovascular disease. The primary outcome of first occurrence of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke occurred in fewer patients in the liraglutide group than in the placebo group. Patients on liraglutide were also at lower risk of death from cardiovascular causes and microvascular events [14]. Although safety analyses were not included in this study because of the

retrospective design, at 24 months significant reductions in SBP, DBP, TC and LDL cholesterol were observed. Furthermore, HDL cholesterol increased significantly from baseline to 24 months. This improvement in blood pressure and lipids, combined with the reductions in weight, supports the findings of the LEADER trial and the positive impact of liraglutide on overall cardiovascular risk. Importantly, around half of the study patients in the current study were prescribed a dose lower than the 1.8 mg dose typically used in the confirmatory clinical trials. By prescribing a lower dose, it is possible that, to some extent, the severity of a number of adverse events associated with liraglutide could be reduced at the expense of the degree of improvements in glycemic control. While this inference is hypothetical and cannot be confirmed by this study, discontinuation in the LEAD trials ranged from 10% to 25%. However, with the exception of LEAD-3, the final follow-up in the LEAD trials was 26 weeks [8–13], whereas in this study, at 4 and 12 months, 81 (6.9%) and 194 (11.3%) patients had discontinued treatment, respectively. This potentially reflects a greater treatment tolerance, owing to the lower dose. At 24 months, 370 (21.5%) patients had discontinued treatment with liraglutide. The rate of discontinuation was lower than that reported after 24 months in the EVIDENCE study (36.2%) [21].

Strengths and Limitations

The relatively large set of patient records analyzed in this study allowed for greater generalizability of the findings in the target population. Conversely, as the study was retrospective and based on the collection of electronic medical records, the completeness of information depended on the ability of participating centers to record clinical data. It should be noted, however, that the completeness of data was satisfactory, and missing data were accounted for during statistical analysis. However, caution should be applied when evaluating the degree of benefit observed with liraglutide in this study, as there was no control for multiplicity.

CONCLUSIONS

Two years of treatment with liraglutide in real-life conditions improved HbA1c, body weight, blood pressure and lipids in patients with T2D to a similar extent of that observed in clinical trials. Such improvements were observed despite a wide range of patient characteristics, doses and treatment modalities. Our data support the use of liraglutide as an efficacious treatment for T2D in clinical practice.

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Compliance with Ethics Guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients before being included in the study.

Data Availability. The data sets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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