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ORIGINAL RESEARCH

Profile of Patients with Diabetes Treated with Insulin Lispro 200 U/ml: A Real-World Study from Spain

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ABSTRACT

Introduction: Insulin lispro 200 U/ml (IL200) is a rapid-acting concentrated insulin used for the treatment of adults with diabetes requiring daily doses of > 20 units of rapid-acting insulin. The aim of this study was to describe the clinical/demographic and treatment characteristics of patients who initiated insulin IL200 therapy in Spain in a real-world setting (PROFILE-IL200).

Methods: This retrospective observational study based on the IQVIA database included adult (≥ 18 years) patients with type 1 (T1D) or type 2 (T2D) diabetes who initiated IL200 between June 2015 and December 2019. Demographic and clinical characteristics were analyzed descriptively.

Results: Main characteristics for the T1D/T2D groups (*N* = 65/167) were as follows: male, 63.1/55.7%; mean (standard deviation [SD]) age, 46.5 (15.5)/62.6 (12.8) years; time since first diabetes record, 6.6 (4.2)/7.9 (2.9) years; body mass index (BMI), 30.9 (5.8)/33.1 (5.5) kg/m^2; glycated hemoglobin, 8.3 (2.1)/8.8 (1.8)%; and diabetes-associated comorbidity, 55.4/92.8%. Among patients with T1D/T2D and a prior diagnosis (*N* = 54/164), 96.3/90.2% had received previous insulin (rapid insulin in 81.5/62.2%), and 13.0/97.6% had received previous noninsulin antihyperglycemic therapy. The mean (SD) total insulin dose before IL200 initiation for T1D/T2D was 98.0 (73.9)/95.2 (59.8) U/day; IL200 was initiated at a dose of 56.3 (43.8)/51.5 (34.3) U/day, with basal insulin in 86.2/83.2% of the patients. IL200 was first prescribed by an endocrinologist or a primary care physician in 48.7% and 46.6% of patients, respectively.

Conclusions: PROFILE-IL200 described the profile of patients treated with IL200 in clinical practice in Spain. Patients were middle-aged, with poor glycemic control, high BMI and associated comorbidities, and received high doses of insulin at IL200 initiation.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13300-022-01264-6.

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PLAIN LANGUAGE SUMMARY

Insulin is one of the main treatments for people with diabetes. More concentrated versions of a fast-acting insulin such as insulin lispro 200 U/ml (IL200) can be better for people with diabetes who need large daily amounts of a fast-acting insulin to keep their blood glucose at appropriate levels, because the injection volume is smaller, and so one IL200 insulin pen lasts longer than other pens. However, there is limited information on the types of patients who start treatment with this type of insulin in the real world. By using a database of medical records, we studied the profile of patients who started treatment with IL200 between 2015 and 2019 in Spain. The study found that patients starting treatment with IL200 were middle-aged, overweight or obese, and with a poor control of blood glucose levels. The patients also had other conditions common in patients with diabetes, such as high blood pressure, high cholesterol and triglycerides, and heart disease, and were receiving high doses of insulin before starting treatment with IL200. Patients were generally prescribed IL200 by their diabetes specialist or general practitioner. The findings of this study could help identify the patients who may benefit the most from the characteristics of IL200, such as a smaller injection volume and longer duration of use for each insulin pen, which may result in patients using IL200 as directed for longer.

Keywords: Diabetes mellitus, type 1; Diabetes mellitus, type 2; Concentrated insulin; Hypoglycemic agents; Insulin lispro; Rapid-acting insulin

Key Summary Points

Why carry out this study?

Insulin lispro 200 U/ml (IL200) is a rapid-acting concentrated insulin used for the treatment of adults with type 1 (T1D) or type 2 (T2D) diabetes requiring daily doses of > 20 units of insulin.

There is limited information available on the sociodemographic and clinical characteristics of patients who are prescribed IL200.

We analyzed the sociodemographic, clinical, and treatment characteristics of patients with T1D and T2D who initiated treatment with IL200 in real-world practice in Spain.

What was learned from the study?

IL200 initiators were middle-aged patients with T1D and T2D with poor glycemic control, high body-mass index, and a high prevalence of diabetes-associated comorbidities.

Often patients were on high doses of insulin before IL200 initiation.

This study presents the profile of patients who may benefit the most from the characteristics of IL200, such as a smaller injection volume and longer duration of use for each insulin pen, which may result in improved adherence.

INTRODUCTION

Insulin was discovered for the treatment of diabetes 100 years ago [1]. Since then, innovation in insulin formulations has greatly expanded therapy options for people with diabetes to include many types of insulins with unique pharmacokinetics and pharmacodynamics and alternative delivery systems [2]. For patients

with type 1 diabetes (T1D), insulin is the mainstay of therapy, and most are treated with multiple daily injections of rapid and basal insulin or with continuous subcutaneous insulin infusion. Most individuals with T1D use rapid-acting insulin analogs to reduce hypoglycemia risk [3].

In contrast, for patients with type 2 diabetes (T2D), pharmacologic treatment often starts with noninsulin antihyperglycemics, and insulin is introduced as the disease progresses or when treatment fails to achieve or sustain glycemic control [4]. Most patients with T2D start with basal, long-acting insulin formulations (glargine, degludec, and detemir), and, eventually, depending on patient needs, use a combination of a long-acting insulin and a rapid-acting insulin at mealtimes (basal-bolus therapy) [3].

Most insulin formulations have a concentration of 100 units/ml (U100), but more concentrated insulin formulations (200 [U200], 200 30/70, 300 [U300], and 500 [U500] units/ml) have also recently become available. The development of concentrated insulins has been driven in part by the epidemic of obesity and T2D [2]. Of the four available concentrated insulins developed to expand therapeutic options for patients, degludec U200 and lispro U200 are bioequivalent to their U100 counterpart, and glargine U300 and human U500 regular insulin are nonequivalent to a 100 U/ml reference formulation [2, 5]. Compared with U100, glargine U300 and human U500 regular insulin have longer duration of action [6]. However, U500 regular insulin has a greater risk of hypoglycemia than U100. The U200 preparations may improve adherence in patients with insulin resistance who require large doses of insulin, as they offer the possibility of delivering more insulin in a lower volume with fewer injections and less pain at the injection site than less concentrated formulations [2–4].

Humalog® 200 units/ml KwikPen (insulin lispro; hereafter IL200) is a rapid-acting concentrated insulin that should be reserved for the treatment of adults with diabetes requiring daily doses of more than 20 units of rapid-acting insulin [7]. IL200 provides the same unit dose in half the injection volume compared with lispro U100, with a similar efficacy and safety profile [8, 9]. In addition to the smaller injection volume for the same dose as its U100 counterpart, advantages of the IL200 pen, which may drive patient preferences, include a longer duration of use for each insulin pen, resulting in fewer pens used than with IL100, and a reduced glide force and glide force variability compared with the IL100 pen [1, 4, 10, 11]. Evidence on the use of IL200 in real-world practice conditions in the post-marketing setting is sparse. A retrospective database analysis of patients in Germany revealed that, as per the summary of product characteristics [7], IL200 is prescribed mainly to people with diabetes who need > 20 U/day of mealtime insulin and that these patients are often older and have obesity and multiple comorbidities [12]. Similarly, a study of a small group of patients with T2D in the UK showed that IL200 users comprised mainly older patients with diabetes complications and poor glycemic control [13]. This study found that the use of IL200 was associated with short-term reductions in glycated hemoglobin (HbA1c) levels and body weight and that it improved patient satisfaction with treatment [13]. A survey among German physicians found that they believed IL200 reduced the injection burden of mealtime insulin for their patients [14].

IL200 has been commercially available in Spain since 2015, but no information is available on the characteristics of patients who are prescribed it, concomitant medication use at therapy commencement, and the doses administered when it is first initiated. The objective of this study was to describe the sociodemographic, clinical, and treatment characteristics of patients with T1D and T2D who initiated treatment with IL200 in real-world practice in Spain.

METHODS

This was a retrospective study conducted using the IQVIA Electronic Medical Records (EMR) database in Spain. The protocol was approved by the Clinical Research Ethics Committee of the Hospital Clínic de Barcelona (Barcelona,

Spain). The study was conducted in accordance with the ethical principles of the Helsinki Declaration of 1964 and its later amendments, good pharmacoepidemiology practices, and the applicable laws and regulations of Spain.

Patients with T1D or T2D (as determined by *International Classification of Diseases, Ninth Edition* [ICD-9] codes) aged ≥ 18 years who started treatment with IL200 from June 1, 2015, to December 31, 2019, were identified in the database and included in the study (Fig. 1). The index date was defined as the date IL200 was first prescribed. Patient sociodemographic and clinical characteristics were derived from available data at the index date or from the last data available before the index date; data on IL200 daily dose and posology and IL200 prescriber at index date were also obtained as well as information on other insulin and noninsulin antihyperglycemic prescriptions at various time points (further details can be found in the Supplementary Materials).

The IQVIA EMR database represents around 3% of the Spanish population (1.2 million people from three geographical regions and including all sexes and age groups). Patient data, both from primary and specialized care, are uploaded and delivered to IQVIA monthly through an electronic link containing the full anonymized data of every patient in participating practices. A full description of the IQVIA database and the potential limitations of the data collected can be found in the Supplementary Materials.

Statistical Analysis

Descriptive analyses were performed to obtain the frequency and proportion for categorical variables and mean, median, and standard deviation (SD) for continuous variables. Analyses were presented overall and by type of diabetes. As part of the analysis, a description of missing data for each variable of interest was provided. Since the IQVIA EMR database only contains data from 2008 onwards, the date of diagnosis of patients diagnosed before 2008 was imputed to the date of first record available for that patient in the IQVIA EMR database and is referred to as time from first diabetes record. The statistical analysis was performed using SAS Enterprise Guide version 7.15.

RESULTS

Patient Demographics and Clinical Characteristics

Of the total population registered in the IQVIA EMR database (N = 1,175,000), 101,348 patients had a diabetes diagnosis (6704 T1D and 94,644 T2D). Of these, 232 patients (65 with T1D and 167 with T2D) were adults who had initiated IL200 between June 1, 2015, and December 31, 2019, and were included in the study (see supplementary information, Figure S1). For patients with T1D, the mean (SD) age was 46.5 (15.5) years, and 63.1% were men (Table 1). For patients with T2D, the mean (SD) age was 62.6 (12.8) years, and 55.7% were men. The majority

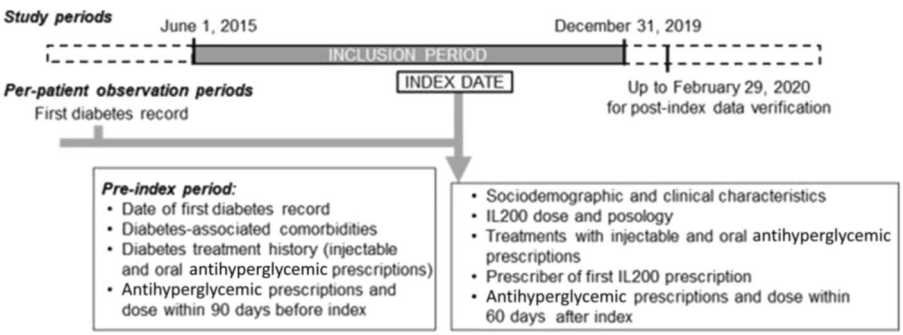

Fig. 1 Study design. The index date was defined for each patient as the start date of treatment with IL200 (between June 1, 2015, and December 31, 2019). IL200, insulin lispro 200 U/ml

Table 1 Patient demographic and clinical characteristics

Variable	T1D (*N* = 65)	T2D (*N* = 167)	Total (*N* = 232)
Age, years, mean (SD)	46.5 (15.5)	62.6 (12.8)	58.1 (15.4)
Age range, years, *N* (%)			
18–39	22 (33.8)	8 (4.8)	30 (12.9)
40–49	18 (27.7)	14 (8.4)	32 (13.8)
50–59	12 (18.5)	46 (27.5)	58 (25.0)
60–69	5 (7.7)	51 (30.5)	56 (24.1)
70–79	7 (10.8)	31 (18.6)	38 (16.4)
≥ 80	1 (1.5)	17 (10.2)	18 (7.8)
Sex (male), *N* (%)	41 (63.1)	93 (55.7)	134 (57.8)
Time from first T1D/T2D record[a], years, mean (SD)	6.6 (4.2)	7.9 (2.9)	7.52 (3.3)
Year of T1D/T2D diagnosis, years, *N* (%)			
2009–2019	37 (56.9)	82 (49.1)	119 (51.3)
≤ 2008	28 (43.1)	85 (50.9)	113 (48.7)
New T1D/T2D diagnoses[b]	11 (16.9)	3 (1.8)	14 (6.0)
BMI[c], kg/m^2, mean (SD)	30.9 (5.8)	33.1 (5.5)	32.6 (5.6)
	N = 37	*N* = 141	*N* = 178
BMI range[c], kg/m^2, *N* (%)	*N* = 37	*N* = 141	*N* = 178
Normal (18.5–24.9)	2 (11.1)	3 (4.8)	5 (6.3)
Overweight (25.0–29.9)	5 (27.8)	14 (22.6)	19 (23.8)
Class I obese (30.0–34.9)	5 (27.8)	16 (25.8)	21 (26.3)
Class II obese (35.0–39.9)	5 (27.8)	16 (25.8)	21 (26.3)
Class III obese (≥ 40.0)	1 (5.6)	13 (21.0)	14 (17.5)
HbA1c[c], %, mean (SD)	8.3 (2.1)	8.8 (1.8)	8.7 (1.9)
	N = 30	*N* = 120	*N* = 150
HbA1c, mmol/mol, mean	67.2	72.7	71.6
Cholesterol[c], mmol/l, mean (SD)	5.4 (1.4)	5.5 (1.5)	5.5 (1.5)
	N = 30	*N* = 114	*N* = 144
HDL[c] mmol/l, mean (SD)	1.4 (0.4)	1.1 (10.3)	1.1 (0.3)
	N = 42	*N* = 89	*N* = 131
LDL[c], mmol/l, mean (SD)	3.3 (1.0)	3.4 (1.1)	3.6 (1.1)
	N = 23	*N* = 72	*N* = 95
Triglycerides[c], mmol/l, mean (SD)	3.5 (2.4)	6.0 (4.2)	5.4 (4.0)
	N = 23	*N* = 79	*N* = 102

Table 1 continued

Variable	T1D (*N* = 65)	T2D (*N* = 167)	Total (*N* = 232)
eGFR[c], ml/min/1.73 m^2, mean (SD)	89.9 (26.1)	76.6 (24.7)	79.47 (25.5)
	N = 33	*N* = 119	*N* = 152
Presence of diabetes-related comorbidities, *N* (%)	36 (55.4)	155 (92.8)	191 (82.3)
Main diabetes-related comorbidities, *N* (%)			
Hypertension	24 (36.9)	114 (68.3)	138 (59.5)
Hyperlipidemia	22 (33.8)	115 (68.9)	137 (59.1)
Macrovascular disease[d]	13 (20.0)	92 (55.1)	105 (45.3)
Microvascular disease[e]	6 (9.2)	8 (4.8)	14 (6.0)
Chronic kidney disease	2 (3.1)	4 (2.4)	6 (2.6)

BMI body mass index, *eGFR* estimated glomerular filtration rate, *HbA1c* glycated hemoglobin, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *SD* standard deviation, *T1D* type 1 diabetes, *T2D* type 2 diabetes

[a]Diagnosis date was unknown for patients diagnosed before 2008. We used the first record in the database for these patients

[b]Patients with a prescription of antihyperglycemic treatment in the 15 days before diagnosis date and no previous antihyperglycemic treatments

[c]Most recent values in the database before index date were used

[d]Includes cardiac ischemic disease, myocardial infarction, acute coronary syndrome, ischemic stroke, peripheral artery disease, congestive heart failure, transient ischemic attack, unstable angina, left ventricular hypertrophy, and left ventricular dysfunction

[e]Includes diabetic retinopathy and microalbuminuria

of patients with T1D (61.5%) were younger than 50 years, whereas the majority (86.8%) of patients with T2D were older than 50 years. For 56.9% of patients with T1D and 49.1% of patients with T2D, diagnosis and IL200 initiation occurred in the period from 2009 to 2019; there was uncertainty about the time since diagnosis to IL200 initiation for the remaining patients. A diagnosis of T1D or T2D occurred at the same time as IL200 initiation in 11 and 3 patients, respectively.

Based on the last record available any time before index date, the mean (SD) BMI was 32.6 (5.6) kg/m^2 (T1D, *N* = 37; T2D, *N* = 141). A high percentage of patients with obesity (BMI $\geq$ 30 kg/m^2) was observed in both diabetes types: 54.1% for patients with T1D and 65.2% for patients with T2D. The overall population presented with poor glycemic control, as shown by the high HbA1c levels (mean, 8.7%, [71.6 mmol/mol]). The percentage of patients with glycemic control (HbA1c $\leq$ 7.0% [53 mmol/mol]) was only 23.3% and 14.2% for patients with T1D and T2D, respectively. It should be noted that the amount of missing data for BMI and HbA1c was relatively large (Table 1).

Comorbidities were present in 55.4% of patients with T1D and in 92.8% of patients with T2D. The most prevalent concomitant diseases in both groups were hypertension and hyperlipidemia (59.5% and 59.1%, respectively, of all patients). Generally, there was a higher prevalence of diabetes-related comorbidities in patients with T2D than in patients with T1D. Hyperlipidemia and hypertension were about twice as frequent in patients with T2D than in patients with T1D, and macrovascular disease was approximately three times as frequent (Table 1).

Table 2 IL200 treatment initiation characteristics

Variable	T1D (*N* = 65)	T2D (*N* = 167)	Total (*N* = 232)
Year of IL200 initiation, *N* (%)			
2015	1 (1.5)	23 (13.8)	24 (10.3)
2016	12 (18.5)	26 (15.6)	38 (16.4)
2017	11 (16.9)	32 (19.2)	43 (18.5)
2018	17 (26.2)	37 (22.2)	54 (23.3)
2019	24 (36.9)	49 (29.3)	73 (31.5)
Prescriber, *N* (%)			
Endocrinologist	35 (53.8)	78 (46.7)	113 (48.7)
Primary care	28 (43.1)	80 (47.9)	108 (46.6)
Oncologist	–	5 (3.0)	5 (2.2)
Internist	–	3 (1.8)	3 (1.3)
Nephrologist	1 (1.5)	–	1 (0.4)
Gastroenterologist	1 (1.5)	–	1 (0.4)
Emergency physician	–	1 (0.6)	1 (0.4)
Daily dose of IL200 in first prescription, *N* (%)	*N* = 65	*N* = 163	*N* = 228
1–19 UI/day	5 (7.7)	36 (22.1)	41 (18.0)
20–49 UI/day	30 (46.2)	53 (32.5)	83 (36.4)
50–99 UI/day	23 (35.4)	58 (35.6)	81 (35.5)
100–149 UI/day	5 (7.7)	14 (8.6)	19 (8.3)
150–300 UI/day[a]	2 (3.1)	2 (1.2)	4 (1.8)
Daily administration, *N* (%)			
Once daily	2 (3.1)	12 (7.4)	14 (6.1)
Twice daily	–	7 (4.3)	7 (3.1)
Three times a day	63 (96.9)	143 (87.7)	206 (90.4)
Four times a day	–	1 (0.6)	1 (0.4)
Daily dose after IL200 initiation, median (P25–P75), UI/kg			
Basal insulin	0.5 (0.4–0.7)	0.6 (0.4–0.8)	0.5 (0.4–0.8)
	(*N* = 35)	(*N* = 125)	(*N* = 160)
Rapid insulin	0.6 (0.4–0.8)	0.5 (0.3–0.8)	0.6 (0.3–0.8)
	(*N* = 37)	(*N* = 144)	(*N* = 181)
Mixed insulin	1.2 (1.2–1.2)	0.5 (0.4–0.8)	0.6 (0.4–1.0)
	(*N* = 1)	(*N* = 9)	(*N* = 10)

Table 2 continued

Variable	T1D (*N* = 65)	T2D (*N* = 167)	Total (*N* = 232)
Total insulin	0.5 (0.4–0.7) (*N* = 35)	0.6 (0.4–0.8) (*N* = 125)	0.5 (0.4–0.8) (*N* = 160)

IL200 insulin lispro 200 U/ml, *T1D* type 1 diabetes, *T2D* type 2 diabetes, *TID* three times a day, *UI* units of insulin
[a]Humalog 150–300 UI/day included the following prescriptions: 50 UI TID (150 UI/day), 60 UI TID (180 UI/day) and 100 UI TID (300 UI/day)

IL200 Treatment Initiation

All 232 patients included initiated IL200 for the first time between 2015 and 2019, with a steadily increasing number of patients starting treatment per year (Table 2). The physicians who issued the first prescription of IL200 were mainly endocrinologists and primary care physicians for both patients with T1D and those with T2D (Table 2). IL200 was prescribed three times daily (TID) to 90.4% of the patients (Table 2), with the most frequent posology being 10 UI TID (9.6%), 20 UI TID (16.2%), and 30 UI TID (9.2%). The mean (SD) daily dose of IL200 at first prescription was 56.3 (43.8) UI for T1D and 51.5 (34.3) UI for T2D. Only 7.7% and 22.1% of patients with T1D and T2D, respectively, were prescribed a daily dose lower than 20 UI.

Antihyperglycemic Prescriptions Before and At/After IL200 Initiation

The prescriptions documented before IL200 initiation among patients previously diagnosed with diabetes (*N* = 218; 54 patients with T1D and 164 patients with T2D) showed that insulin was prescribed to 96.3% and 90.2% of patients with T1D and those with T2D, respectively (Fig. 2a, Table S1). In total, 13% of patients with T1D received noninsulin treatments, with prescriptions recorded for metformin and sodium glucose co-transporter 2 (SGLT2) inhibitors (Table S1). To describe antihyperglycemic treatment immediately prior to IL200 initiation, a time window of 90 days for availability of prescriptions was considered. In the 90 days before starting IL200, 59.3% of patients with T1D and 39.6% of patients with T2D had already received rapid insulin (26.6% and 9.8% of patients with T1D and T2D, respectively, received Humalog 100) (Table S2). Similar to the overall pre-IL200 period, the noninsulin treatments prescribed to 9.3% of patients with T1D were metformin and SGLT2 inhibitors (Table S2). Analysis of antihyperglycemic treatments concomitantly prescribed with IL200 (at index or within 60 days after IL200 initiation) showed a high percentage of patients receiving basal insulin (86.2% for T1D and 83.2% for T2D) and 16.9% of patients with T1D and 72.5% of those with T2D receiving oral antihyperglycemic agents (Fig. 2c and Table S3). Again, metformin and SGLT2 inhibitors were the noninsulin treatments prescribed to patients with T1D (Table S3).

Daily Dose of Insulin

The mean daily doses of the different types of insulin showed that patients were on high doses of rapid insulin before IL200 initiation: 64.6 UI (0.8 UI/kg) and 68.4 UI (0.7 UI/kg) for patients with T1D and those with T2D, respectively (Fig. 3). After IL200 initiation, for patients with T1D, the mean daily dose was 44.7 UI for basal insulin (*N* = 56), 56.3 UI for rapid insulin (*N* = 65), and 90.0 UI for mixed insulin (*N* = 2) (see Table 2 for median UI/kg/day values). The total daily dose of insulin (including IL200) was 97.6 UI (*N* = 65). Among patients with T2D, mean daily dose was 54.9 UI for basal insulin (*N* = 139), 51.7 UI for rapid insulin (*N* = 167), and 56.7 UI for mixed insulin (*N* = 10). The total daily dose of insulin (including IL200) was 99.8 UI (*N* = 167). These results indicate that

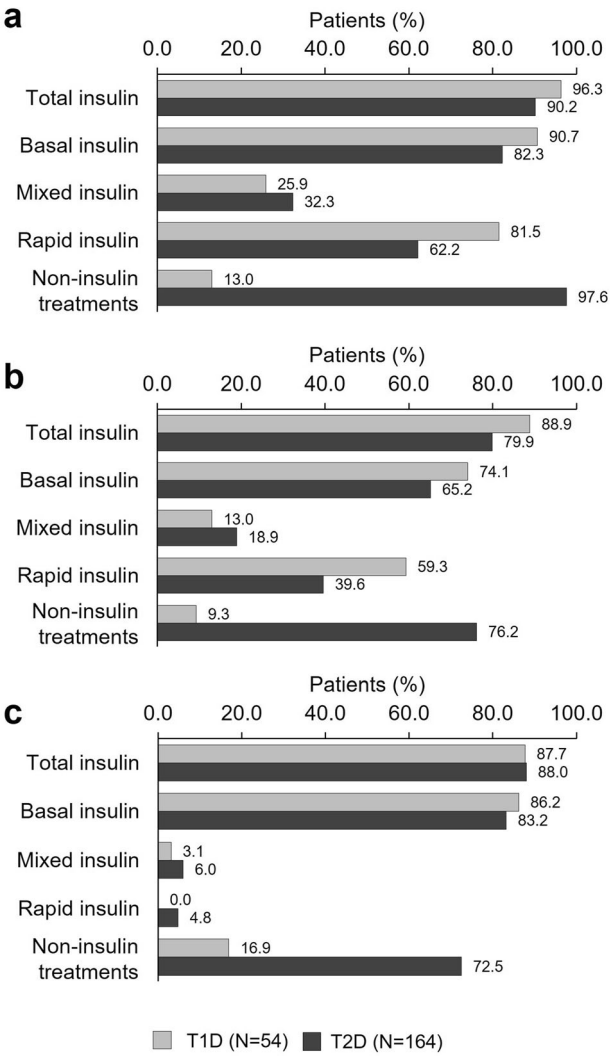

Fig. 2 Medication prescribed to patients before and after IL200 initiation. **a** Antihyperglycemic prescriptions any time before IL200 initiation (patients with new diagnosis [$N = 14$] excluded). **b** Antihyperglycemic prescriptions 90 days before IL200 initiation. **c** Antihyperglycemic prescriptions at or within 60 days of IL200 initiation (excluding IL200). Total insulin refers to all types of insulin. Noninsulin treatments included oral and injectable drugs (see Tables S1 and S2). IL200, insulin lispro 200 U/ml; T1D, type 1 diabetes; T2D, type 2 diabetes

the total dose of insulin was similar before and after initiation of IL200.

DISCUSSION

To our knowledge, this is the first study to describe the profile and treatment patterns of patients initiating IL200 in real-world clinical practice in Spain. It showed that patients with T1D and T2D who were prescribed IL200 generally presented with poor glycemic control, a high BMI, and diabetes-associated comorbidities and were receiving high doses of insulin at IL200 initiation. This patient profile is aligned with previous observational studies of IL200 in other European countries [12, 13].

Data for this study were derived from an EMR database in which 8.6% of the patients registered had diabetes, which was relatively

comparable to the estimated prevalence in Spain (10.5%) [15]. Also, 80.6% of the patients with T2D in the database were treated with diabetes therapies, similar to findings of a study of patients receiving treatment in a large region of Spain (81.6% in 2013) [16]. These parameters suggest that the database was largely representative of the population at the national level. The mean ages of the patients starting IL200 in the study differed according to whether they were diagnosed with T1D or T2D, reflecting the characteristic courses of these two forms of the disease. The largest age group of patients was 18–39 years for those with T1D and 60–69 years for those with T2D. Patients with T1D cannot be compared with other real-world studies of patients receiving IL200, as these mostly or only comprised patients with T2D [12, 13].

Most patients with T1D and T2D presented with high HbA1c levels at the time of IL200 initiation, suggesting that they were prescribed this drug when their disease was not well controlled, although many values for HbA1c were missing, which may have reduced the precision of the determination of HbA1c in our patient group. Most patients also had a high BMI, similar to IL200 initiators in the UK [13] and in patients from Germany, where IL200 is

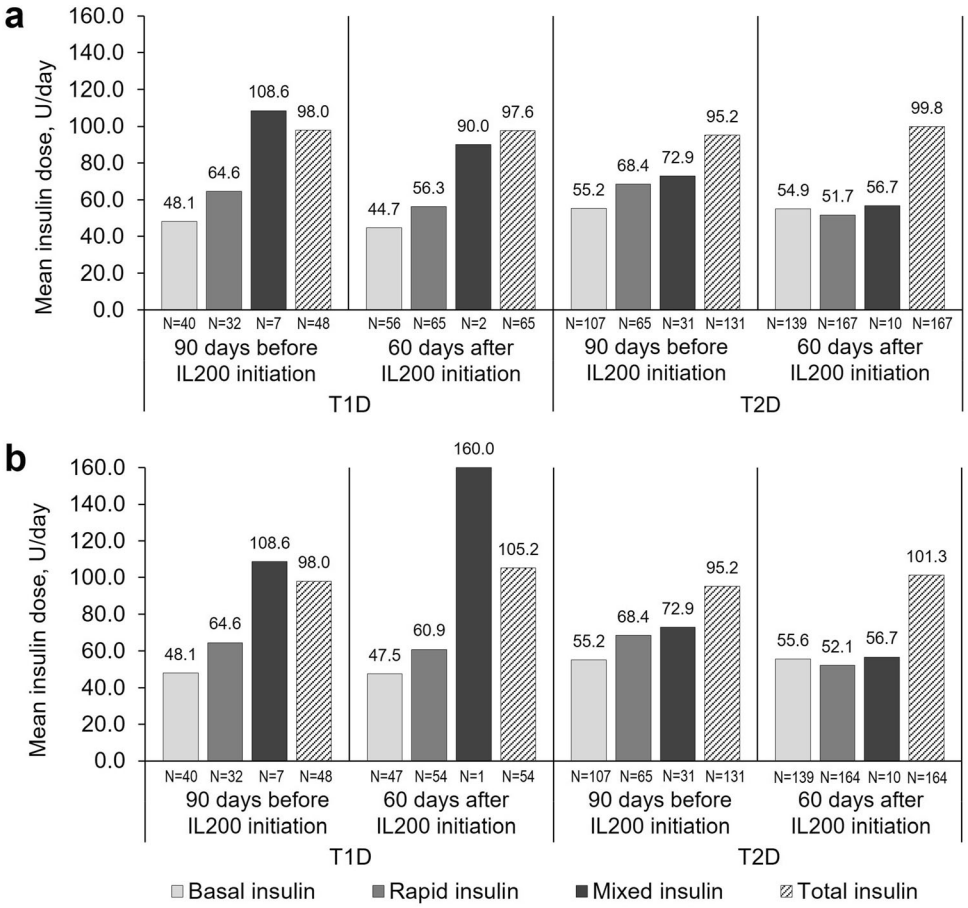

Fig. 3 Mean daily dose of insulin prescribed within 90 days before and within 60 days after IL200 initiation. The mean daily dose of individual insulin types was based on the number of patients using each insulin type, whereas the total daily dose was based on all patients using any insulin. Mean doses were calculated based on the number of patients with valid doses available. **a** All patients; **b** excluding patients with newly diagnosed diabetes. *IL200* insulin lispro 200 U/ml, *T1D* type 1 diabetes, *T2D* type 2 diabetes

implemented mainly for people with obesity and T2D receiving prandial-insulin-only regimens [12]; again, as for HbA1c, our study had substantial missing data for BMI, which might have biased the sample towards more extreme values.

Diabetes-related comorbidities were present in about half of the patients with T1D (55.4%) and in most patients with T2D (92.8%), a difference that could likely be explained by the age differences between the groups. In both cases, however, hypertension and hyperlipidemia were the most prevalent comorbidities, followed by cardiovascular disease. High rates of multimorbidity were also observed in the populations from the studies in the UK and Germany [12, 13].

IL200 was overwhelmingly prescribed by endocrinologists (48.7%) and primary care physicians (46.6%) for both patients with T1D and those with T2D. However, it is likely that the high percentage of prescriptions by primary care physicians could reflect the fact that, in Spain, although antihyperglycemic therapy is established by the endocrinologist, it is the primary care physician who ultimately signs the prescriptions and provides routine follow-up care to the patient.

This study shows that most patients with T1D (81.5%) were already taking rapid insulin before IL200 initiation (16.5% of patients with T1D had new prescriptions). This was expected, as a prandial insulin is always part of a T1D therapy regimen [3]. Conversely, very few patients with T1D (13.0%) were taking noninsulin treatments in addition to insulin, as per standard practice in Spain, whereas almost all of the patients with T2D were (97.6%). Metformin, alone or in combination, was the mainstay of the treatment for most patients with T2D before IL200 initiation, but the proportion of metformin users was reduced (86.0% vs. 53.3%) after IL200 initiation, suggesting that IL200 was prescribed in the context of intensification of the T2D therapy regimen. At first prescription, mean (SD) daily doses of IL200 in the study population were 56.3 (43.8) UI for patients with T1D and 51.5 (34.3) UI for patients with T2D, with a maximum of 300 UI per day and up to 90% receiving IL200 TID. In contrast, the study of UK patients initiating IL200 reported average daily doses three times higher (mean [SD] 154.3 [104.1] UI), also mostly administered TID on commencement [13]. In our study, patients were on high doses of insulin at IL200 initiation, a characteristic profile of the patients that could benefit most from this rapid insulin formulation. Little information is available on the specific reasons why physicians prescribe IL200. A study of German physicians' perceptions showed that they felt their patients considered IL200 convenient to use and easily self-administered once the patient was instructed on how to switch from the U100 formulation [14]. Physicians considered each patient's medical needs and nonclinical preferences and were confident that their patients would be adherent to their mealtime insulin treatment regimen when on IL200. In the German study, physicians reported that 44% of their patients received daily IL200 doses of 20–50 UI, 26% received doses of 50–100 UI, and 8% received $>$ 100 UI [14]. These observations are consistent with those in the present study, where 71.9% of the total studied population were prescribed 20–100 UI/day.

This study has some limitations that should be taken into account when considering the results, mostly because of the retrospective nature of the design and the use of an existing EMR as the data source. EMR databases are often limited by missing data, heterogeneity of data quality, and variability in the frequency of data capture and coverage for key study-related parameters. For example, the specialists who issued the first prescription of IL200 were mainly endocrinologists, followed by primary care practitioners. The high proportion of primary care practitioners prescribing IL200 in the study could be related to their high representation in the EMR IQVIA database and, as mentioned previously, that they were likely following the therapeutic strategy set by the endocrinologists. In addition, the physicians included in the database may not be fully representative of the physicians treating patients with diabetes in Spain, as participation in the database and data collection is optional. These physicians (and subsequently their patients) may differ from those who do not contribute,

resulting in potential selection bias. Another limitation is that, given the nature of real-world data, and because of variabilities in efficiency and completeness of records, there were instances of missing data. For example, although the patients included in the study had a high BMI and therefore the insulin doses would be better described as U/kg, the amount of missing data and the fact that the data often would not include the body weight at the time of prescription limits the interpretation of these values. In addition, the IQVIA EMR database contains information on diagnosis only since 2008 (full prescription records have only been collected in the database since 2013), and therefore duration of diabetes could not be determined for some patients. Finally, since only data in the IQVIA EMR database were analyzed, no information on quality of life measures or adherence for these patients was available for analysis. Measuring changes in HbA1c over time was also outside of the scope of the present study, which was designed to describe the profile of patients at IL200 treatment initiation.

Despite these limitations, the study analyzed sufficient data on the profile of patients with T1D and T2D in a short period of time and from a large number of centers. Although randomized clinical trials are essential to analyze specific aspects of drug efficacy and safety [17], observational studies such as this are complementary and reveal the real-world patterns of patient characteristics and treatments. Future real-world studies should be conducted focusing on glycemic outcomes and changes in patient satisfaction, quality of life, and adherence to the treatment following IL200 initiation.

CONCLUSIONS

IL200 initiators in the real world in Spain were mainly middle-aged patients with T1D and T2D with poor glycemic control, high BMI, and a high prevalence of diabetes-associated comorbidities. The sociodemographic and clinical characteristics were generally aligned with previous observational studies of IL200 conducted in other countries. As expected, there were differences between those with T1D and T2D (patients with T1D were younger and had fewer comorbidities and a lower BMI than those with T2D). Patients were on high doses of insulin before IL200 initiation. This study presents the profile of patients who may benefit the most from the characteristics of IL200, such as a smaller injection volume and longer duration of use for each insulin pen, which may result in improved adherence.

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Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available due to the database used being available only for commercial use, and not directly accessible by third parties.

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