

BMJ Open Characteristics of patients with type 2 diabetes mellitus newly treated with GLP-1 receptor agonists (CHADIG Study): a cross-sectional multicentre study in Spain

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ABSTRACT

Objective: Several glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1Ra) have been made recently available in Spain for type 2 diabetes mellitus (DM2) treatment. There are no published data on the clinical and sociodemographic profile of patients initiating treatment with GLP-1Ra in Spain. Our objective was to understand these patients' characteristics in a real-world clinical practice setting.

Design: Cross-sectional observational study.

Setting: Spanish specialist outpatient clinics.

Participants: 403 adults with DM2 initiating GLP-1Ra treatment were included.

Primary and secondary outcome measures:

Sociodemographic and DM2-related clinical data, including treatment at and after GLP-1Ra initiation and comorbidities, were collected.

Results: Evaluable patients (n=403; 50.9% female) were included (July 2013 to March 2014) at 24 centres by 53 specialists (47 endocrinology, 6 internal medicine), with the following profile (value±SD): age (58.3±10.4 years), diabetes duration (9.9±7 years), body mass index (BMI; 36.2±5.5) and glycated haemoglobin (HbA1c; 8.4±1.4%); 14% had HbA1c≤7%. Previous antidiabetic treatment: 53.8% only oral antidiabetic drugs (OADs), 5.2% insulin and 40% insulin and OAD; of those receiving OAD, 35% single drug, 38.2% 2 drugs and 24% 3 drugs. Concomitant to GLP-1Ra, 55.3% were only on OAD, 36.2% on insulin and OAD, and 7.2% only on insulin. Of those receiving OAD, the GLP-1Ra was mainly associated with 1 drug (65%) or 2 drugs (31.8%). GLP-1Ra are frequently added to existing antidiabetic drugs, with dipeptidyl peptidase-4 inhibitors being the OAD most frequently switched (45% receiving 1 before starting GLP-1Ra, only 2.7% receiving it concomitantly).

Conclusions: In Spain, GLP-1Ra therapy is usually started in combination with OADs or OADs and insulin. These drugs are used in relatively young patients often not reaching therapeutic goals with other treatment combinations, roughly a decade after diagnosis and with a relatively high BMI. The latter could be explained

Strengths and limitations of this study

- To the best of our knowledge, this is the first cross-sectional effort trying to find out the profiles of patients receiving initial prescriptions of glucagon-like peptide-1 receptor agonists (GLP-1Ra), since efforts so far have been largely limited to retrospective analyses or physician surveys.
- The study sample is fairly representative of the overall Spanish population of patients with type 2 diabetes mellitus.
- The reason for treatment change was not recorded. Therefore, the reasons for prescribing GLP-1Ra cannot be fully ascertained.
- Payers' restrictions to GLP-1Ra in Spain resulted in first prescription being mainly done by specialists, which may have resulted in some patient selection bias towards a more advanced, complex patient type.

by Spanish regional payers limiting reimbursed prescription to patients with a minimum BMI threshold (>30 in most regions, >35 in some).

INTRODUCTION

Type 2 diabetes mellitus (DM2) is a chronic metabolic disorder with worldwide steadily increasing prevalence that is expected to grow in all age groups worldwide from 2.8% in 2000 to 4.4% in 2030.¹ In Spain, the overall prevalence of diabetes mellitus in adults adjusted for age and sex was estimated in a representative sample of the population to be 13.8%, of which about half (6.0%) had unknown diabetes² and, considering the Spanish population, the number of patients with diagnosed diabetes (treated or



untreated with drugs) may be estimated to be over 3.6 million people. Total (known and unknown) DM2 prevalence in Spain was estimated at 15.3% in men and 14.2% in women.³

The short-term aim of therapy for hyperglycaemia is improved blood glucose control without significant tolerability or safety issues, and with the longer term objective of reducing vascular damage. Although most initial pharmacological therapies include an oral glucose-lowering agent, a steady decline in islet β -cell function results in progressive hyperglycaemia, which requires a stepwise escalation of treatment. Eventually, insulin is often required as the only therapy independent of the need for endogenous insulin production. Glucagon-like peptide-1 receptor agonists (GLP-1Ra) have recently become a therapeutic option. GLP-1Ra mimic, at supra-physiological levels, the action of endogenous GLP-1, in stimulating glucose-dependent insulin secretion and by suppressing glucagon secretion. Gastric emptying is delayed, especially in the early weeks of therapy. This, and perhaps a direct or indirect hypothalamic action, results in appetite/satiety changes and thus loss of body weight.⁴

Despite being on the market since several years, little is known about the characteristics of patients treated with GLP-1Ra and about the place of these drugs in DM2 in the real-life setting. In fact, we could not find any prospective study aiming at finding out these aspects, which may be quite relevant. The published literature includes several efforts using retrospective analyses of existing databases⁴⁻⁷ or physician surveys.⁸ Furthermore, current available databases do not provide this information for patients in Spain and in most other countries. Hence, the present cross-sectional study was conducted in a real practice environment with the objective of finding and describing the demographic and clinical characteristics of patients with DM2 who receive initial prescriptions of a GLP-1Ra in Spain for the treatment of DM2 and, as such, constitutes a novel approach which may be valuable in learning about the patient profiles and the decision drivers of treating physicians to initiate therapy with a GLP-1Ra, something which indeed may vary depending on the countries and circumstances.

PATIENTS AND METHODS

Study design

This was a cross-sectional, observational, non-interventional, multicentre study conducted in adult patients with DM2 newly treated with GLP-1Ra in Spanish specialist outpatient clinics, since these drugs are mostly initiated in Spain by specialists. The study was approved by Research Ethics Committees from participating centres and was conducted according to the Declaration of Helsinki. All patients signed informed consent.

Study population

Participating physicians were invited to record characteristics of consecutive patients attending outpatient

specialist clinics since in Spain initial prescriptions of GLP-1Ra are mostly made by specialists across the country. Patients were included in the study if they: (1) were adults (≥ 18 years old) presenting with DM2 and visiting the investigator for any reason; (2) were prescribed for the first time a GLP-1Ra on the day of inclusion in the normal course of care, or who had initiated GLP-1Ra therapy within 3 months before the inclusion visit (as long as the study required information was available); and (3) provided informed consent in writing to participate. Candidate patients were excluded if they were participating in a study with an investigational drug or procedure.

A sample size of 384 patients was required in order to estimate in the study population, with a CI (95%) of $\pm 5\%$, a 50% proportion of one of the two main criteria of interest, body mass index (BMI) or glycated haemoglobin (HbA1c) level at initiation of GLP-1Ra therapy. Assuming a 5% rate of non-evaluable cases, 400 patients had to be enrolled. Patient inclusion took place during the period between July 2013 and March 2014. No interventional procedure or change in practice was required.

Measurements

Main variables of interest were BMI and blood HbA1c level when initiating GLP-1Ra. Other study variables included demographic characteristics (age, gender), weight, height, arterial blood pressure, tobacco use, latest available clinical data (year of DM2 diagnosis, year of first antidiabetic treatment, DM2-related complications and comorbidities) prior to GLP-1Ra treatment, name, dosing schedule and date of first prescription of GLP-1Ra, HbA1c target at initiation, antidiabetic treatments before initiating GLP-1Ra and simultaneously to the GLP-1Ra and latest available biological laboratory results (lipid and renal balance) before GLP-1Ra.

Statistical analysis

Description of study results is shown as mean (SD) values or as percentages with ranges and/or 95% CIs, as applicable.

Relevant statistical tests were used to compare subgroups depending on type of data. For categorical data, group comparisons were performed by χ^2 provided that the number of cases for each modality was >5 ; otherwise, Fisher's exact tests were performed. For continuous data, Student's t-test was used after having checked for required data assumptions.

RESULTS

In total, 403 evaluable patients were included by 53 investigators (47 endocrinologists and 6 internal medicine specialists) from 24 outpatient clinics; study sites were located at 10 out of 17 Spanish administrative regions (autonomous communities). Patients' characteristics are shown in [table 1](#). The mean (SD) age of patients with DM2 was 58.32 (10.4) years, 205 (50.9%)

Table 1 Sociodemographic and clinical characteristics and treatments of patients before initiating GLP-1Ra treatment

Age, years, mean (SD)	58.32 (10.4)
Sex, male, N (%)	198 (49.1)
Weight, kg, mean (SD)	97.59 (17.9)
Height, cm, mean (SD)	164.0 (10.0)
BMI, kg/m ² , mean (SD)	36.22 (5.5)
Normal 18.5–25, N (%)	1 (0.2)
Overweight 25–30, N (%)	24 (6.0)
Obese ≥30, N (%)	378 (93.8)
Waist size, cm, mean (SD)	114.28 (15.0)
Systolic/diastolic blood pressure, mm Hg, mean (SD)	140.55 (18.0)/80.35 (10.0)
Smoking habit, N (%)	
Current	55 (13.6)
Former	136 (33.7)
Never smoked	212 (52.6)
Glycaemic control	
Fasting blood glucose, g/L, mean (SD)	1.77 (0.6)
HbA1c %, mean (SD)	8.41 (1.4)
HbA1c <6.5%, N (%)	24 (6.0)
HbA1c 6.5–7%, N (%)	33 (8.2)
HbA1c 7–8%, N (%)	130 (32.3)
HbA1c >8%, N (%)	216 (53.6)
Lipid parameters, mean (SD)	
Total cholesterol (g/L)	1.8 (0.4)
HDL cholesterol (g/L)	0.43 (0.1)
LDL cholesterol (g/L)	1.01 (0.3)
Triglycerides (g/L)	1.95 (1.4)
Creatinine clearance, mL/min, mean (SD)	88.9 (24.1)
Normal ≥90, N (%)	160 (46.8)
Mild renal impairment 60–90, N (%)	145 (42.4)
Moderate renal impairment 45–60, N (%)	30 (8.8)
Moderate renal impairment 30–45, N (%)	7 (2.0)
DM2 history	
Time since diagnosis (years), mean (SD)	9.91 (7.0)
Age at diagnosis (years), mean (SD)	48.35 (10.3)
Time between DM2 diagnosis and first treatment, N (%)	
Concomitant	261 (81.1)
1 year	18 (5.6)
1–5 years	31 (9.6)
>5 years	12 (3.7)
Antidiabetic treatment before/after initiation of GLP-1Ra	
OAD only, N (%)	217 (53.8)/223 (55.3)
OAD only, 1 drug, N (%)	76 (35.0)/0
OAD only, 2 drugs, N (%)	83 (38.2)/145 (65.0)
OAD only, 3 drugs, N (%)	52 (24.0)/71 (31.8)
OAD only, ≥4 drugs, N (%)	6 (2.8)/7 (3.1)
Insulin only, N (%)	21 (5.2)/29 (7.2)
OAD+insulin, N (%)	161 (40.0)/146 (36.2)
No antidiabetic drugs, N (%)	4 (1.0)/5 (1.2)

BMI, body mass index; DM2, type 2 diabetes mellitus; GLP-1Ra, glucagon-like peptide-1 receptor agonists; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OAD, oral antidiabetic drug.

were female and most (96.3%) were born in Spain; all participants had to be fluent in Spanish. DM2 diagnosis was performed 9.92 (7.0) years before GLP-1Ra initiation, mean age at diagnosis was 48.35 (10.3) years and 66.7% used home glucose monitoring with an average of 8.78 (7.6) strips per week.

Most (90.8%) patients presented with at least one current or past self-declared complication or comorbidity and 47.3% were current or former smokers. Hypertension was present in 71.2% of patients (treated in 95.1% of them) and 70.2% had currently treated dyslipidaemia. Other most frequent complications or patient-declared comorbidities included renal dysfunction (microalbuminuria in 18.4%, chronic renal insufficiency in 3.2%, proteinuria in 2.5%), ocular disease (diabetic retinopathy in 13.2%), macrovascular complications (myocardial infarction or ischaemic heart disease in 13.2%, peripheral vascular disease in 4.5% or stroke in 3.5%) and peripheral neuropathy (5.7%).

At the time of the initiation of GLP-1Ra therapy, the mean (SD) BMI was 36.2 (5.5) kg/m². As shown in [table 1](#), most patients (93.8%) were obese and showed a high mean waist size (114.28 cm).

Mean systolic and diastolic blood pressure values were 140.6 and 80.4 mm Hg, respectively, with 43.6% of patients above the WHO-recommended⁹ cut-off for hypertension diagnosis (>140 mm Hg systolic or >90 mm Hg diastolic).

With regard to the drug prescribed, liraglutide was initiated in 48.6%, lixisenatide in 35.0%, weekly exenatide in 12.9% and daily exenatide in 3.5% of patients ([table 2](#)).

Fasting blood glucose at GLP-1Ra initiation was available in 92.6% of patients with a mean value of 1.77 g/L (0.6). Mean HbA1c at GLP-1Ra initiation was 8.4% (1.4) and in 53.6% of patients it was higher than 8%, while it was ≤7% in 14.2% of the participants. Interestingly, patients with HbA1c ≤7%, as compared with the rest of the study population, had a higher mean BMI (38.7 vs 35.8, $p<0.001$), were more often treated only with oral antidiabetic drugs (OADs) before GLP-1 analogue initiation (70.2% vs 51.2%, $p=0.0076$), and more frequently receiving OAD treatment in monotherapy (50% vs 31.6%, $p=0.0279$). Patients with HbA1c ≤7% before initiating GLP-1Ra, as compared with the rest of the study population, were more often prescribed weekly exenatide (29.8% vs 10.1%, $p=0.0004$) and, conversely, less lixisenatide (14.0% vs 38.4%, $p=0.0003$). Also, they mostly received GLP-1Ra in addition to OAD only (73.7% vs 53.8%, $p=0.0049$), and received less mixed treatment (OAD+insulin, 22.8% vs 38.4%, $p=0.0229$).

With respect to the lipids profile, mean values were 1.8 (0.4) g/L for total cholesterol, 0.43 (0.1) g/L for high-density lipoprotein (HDL) cholesterol, 1.01 (0.3) g/L for low-density lipoprotein (LDL) cholesterol and 1.95 (1.4) g/L for triglycerides ([table 1](#)).

Renal function tests showed a mean creatinine clearance of 88.9 (24.1) mL/min; 42.4% of patients

Table 2 GLP-1Ra (glucagon-like peptide-1 receptor agonists) initiated and unit dose

GLP-1Ra	Dose	Number of patients (% for each drug)
Liraglutide	0.6 mg	29 (14.8)
	1.2 mg	126 (64.3)
	1.8 mg	41 (20.9)
Lixisenatide	10 µg	43 (30.5)
	20 µg	98 (69.5)
Weekly exenatide	2 mg	52 (100)
Exenatide	5 µg	1 (7.1)
	10 µg	13 (92.9)

Table 3 OAD used before and after GLP-1Ra treatment initiation

Number of OAD	n=217 Before GLP-1Ra	n=223 With GLP-1Ra
1	76 (35.0%)	0
2	83 (38.2%)	145 (65.0%)
3	52 (24.0%)	71 (31.8%)
>3	6 (2.8%)	7 (3.1%)
Mean number of OAD (SD)	1.94 (0.8)	2.39 (0.6)
Biguanide		
Metformin	199 (91.7%)	214 (96.0%)
Sulfonylurea		
Gliclazide	47 (21.7%)	41 (18.4%)
Glimepiride	21 (9.7%)	18 (8.1%)
Glibenclamide	9 (4.1%)	—
Other	2 (1.0%)	2 (0.8%)
DPP-4 inhibitor		
Sitagliptin	57 (26.3%)	2 (0.9%)
Vildagliptin	33 (15.2%)	3 (1.3%)
Other	8 (3.7%)	1 (0.4%)
Mitiglinide		
Repaglinide	30 (13.8%)	15 (6.7%)
Glitazone		
Pioglitazone	13 (6.0%)	11 (4.9%)
α glucosidase inhibitor		
Acarbose	1 (0.5%)	—

DPP-4, dipeptidyl peptidase-4; GLP-1Ra, glucagon-like peptide-1 receptor agonists; OAD, oral antidiabetic drug.

presented with mild (60–90 mL/min) and 10.8% with moderate (30–60 mL/min) renal impairment (table 1).

The first use of antidiabetic drugs was usually concomitant to diagnosis (81.1% of patients). At study visit, before GLP-1Ra initiation, 53.8% of patients were receiving only an OAD treatment and 40% had a mixed treatment with insulin and OAD. In total, 5.2% were only treated by insulin. Of patients only on OAD, most were treated with two drugs (38.2%) or a single drug (35%), and 24% received triple therapy (table 1).

At GLP-1Ra initiation, the most frequent (90.7% of patients) individualised HbA1c target was 7%; however,

this could only be recorded from 33% of study participants. GLP-1Ra were mostly prescribed without any change in the main classes of previous antidiabetic therapies (table 1). In addition to the GLP-1Ra, more than half of the patients (55.3%) received only an OAD, 36.2% had a mixed treatment with insulin and OAD, and only 7.2% were treated with insulin without OAD. Mainly, types of antidiabetic treatments prescribed with the GLP-1Ra were similar to those used before its initiation (table 3), but some patients already treated with three drugs stopped one of their OAD (most frequently dipeptidyl peptidase-4 inhibitors). Finally, the GLP-1Ra were most frequently prescribed with two OAD (65%) or with three OAD (31.8%); some patients (3.1%) received four different OAD or more.

DISCUSSION

This study provides demographic and clinical profiles of patients with DM2 at the time of initiation of treatment with GLP-1Ra, as well as drug treatment for DM2 before and after initiation of GLP-1Ra in real-life clinical practice in Spain. Study investigators were all specialists (endocrinology and internal medicine) representing the usual setting where GLP-1Ra treatments are initiated in Spain, and participating centres were spread across the country covering 10 out of 17 administrative regions (autonomous communities). Thus, it seems reasonable to assume that the study sample is fairly representative of the overall country population of patients with DM2 who were being prescribed GLP-1Ra for the first time during the study period.

Patients' characteristics differ somehow from the average DM2 Spanish population, as compared with recent epidemiological data.^{10–12} Our patients were younger (58.3 years), with just a slightly higher proportion of females (50.9%), more with obesity (93.8%) and high mean BMI (36.2 kg/m²), as well as mean arterial blood pressure (140.6/80.4 mm Hg); more showed renal dysfunction (53.2%) and poor lipid balance (HDL cholesterol <0.5 g/L and LDL cholesterol ≥1 g/L); also, time since DM2 diagnosis was longer (9.9 years) and almost all participants were on antidiabetic pharmacological treatment before initiating GLP-1Ra. Glycaemic control was also poor with mean fasting glycaemia of 1.8 g/L and 85.9% of participants showing HbA1c >7%. Since the reason for treatment change was not recorded (eg, poor tolerability, compliance issues, patient's request, etc), the reasons for prescribing GLP-1Ra to patients with HbA1c ≤7% (14.1%) cannot be fully ascertained. However, there are several intriguing findings (higher use of weekly exenatide, lower use of lixisenatide, higher BMI, higher use of OAD therapy in addition to the GLP-1Ra) that could suggest an aim of weight loss as a primary driver for use, rather than pursuing more glycaemic control with weight loss being an added benefit. In addition, with regional payers in Spain limiting reimbursed prescription of GLP-1Ra to patients with BMI above 30 (or 35 kg/m² in some regions) and with

so much emphasis put on the weight reduction potential of this class of drugs, the possibility that this has become a major factor for use in this subgroup cannot be ruled out.

With respect to antidiabetic treatment prior to GLP-1Ra initiation, a proportion of study participants were receiving insulin, either in combination with OAD or as single treatment. Compared with the average patient with DM2 in Spain, this proportion (45%) is remarkably higher than recently published data (23%),¹⁰ further reflecting that the patients' profiles from our study population represent a subset of DM2 individuals with a longer duration of the disease, who are less responsive to antidiabetic treatment, with a more severe disease course and/or less compliant with disease management, among other possible explanations. All the above characteristics seem to describe a typical patient with DM2 with a longer disease course, more risk factors (obesity and high BMI) and more diabetes-related comorbidities (hypertension, renal dysfunction, hyperlipidaemia) than in the average patient with DM2. In Spain, indications for use of GLP-1Ra, as described in the approved prescribing information,^{13–16} recommend its use when patients do not achieve glycaemic control with full doses of any, among various, OAD without mentioning other specific patients' characteristics or restrictions (except for moderate or severe renal dysfunction, hepatic impairment and use in children). However, these data show that Spanish physicians are initiating GLP-1Ra mostly in advanced DM2 cases, especially in overweight or obese individuals, reflecting current Spanish regional payers' restrictions on GLP-1Ra reimbursed prescription only to patients with a BMI >30 or >35 kg/m². In terms of duration of diabetes, this would appear to be in contrast with some recent physician survey in the UK,⁸ where it would appear that GLP-1Ra are used in patients with a shorter duration of diabetes. In that survey, the importance of the need for further glycaemic control and weight loss is in line with the findings of the present study.

With respect to the choice of GLP-1Ra among available drugs in Spain at the time this study was conducted, it should be noticed that two compounds from this class were launched while this study was recruiting patients, weekly exenatide, followed by lixisenatide some time later. Despite its apparent advantage with weekly dosing versus other GLP-1Ra, weekly exenatide was prescribed to 13% of study participants while lixisenatide, which requires daily injections, was initiated in 35% of patients. Liraglutide, older in the market and also administered as daily injections, was also highly (49%) prescribed during this study. This, together with the substantial number of individuals receiving insulin in combination with GLP-1Ra, could explain why GLP-1Ra compounds which are approved to be used in combination with insulin, such as lixisenatide and liraglutide, were prescribed more often in this cohort.

Real-life studies are deemed necessary to complement information retrieved with clinical trials. Both have

limitations and should be seen as complementary. It is important to understand the strengths and weaknesses of both approaches. The choice of the investigators, the lack of a centralised laboratory, the lack of intensive monitoring among others, hamper the internal validity of real-life studies. The sites and investigators for this study were selected on the basis of being current users of GLP-1Ra and being able to achieve reasonably short start-up times. However, the number of sites and the fact that more than 50% of the Spanish autonomous communities (including those with larger populations) were included should provide a fair representativeness of the country's reality. Owing to the existence of payers' restrictions to GLP-1Ra use in Spain, first prescription of these compounds by the primary care physicians was clearly minor at the time of conducting the study. Hence, the predominance of specialist sites may have resulted in some patient selection bias towards a more advanced, complex patient type. However, most guidelines and algorithms tend to place GLP-1Ra late in the course of the disease, mainly for cost reasons, and most pivotal clinical trials of currently available studies have been conducted with patients with a long duration of diabetes, so the bias may not have had as much impact as could be anticipated.

On the other hand, this study is the first effort to assess the clinical and sociodemographic profile of patients receiving an initial prescription of GLP-1Ra in Spain, in a relevant number of patients and sites. Moreover, its cross-sectional nature brings a new and different perspective since the published data so far come from retrospective analyses of databases mostly aiming at assessing comparative efficacy, or from physician surveys providing perceptions of what is behind the decision to prescribe or not a GLP-1Ra. As such, it should provide valuable insight in learning about such treatment patterns.

In conclusion, this study provides an updated description of patients with DM2 initiating GLP-1Ra treatment in Spain. Their worse than average clinical picture of patients with DM2 probably reflects clinicians' behaviour towards limiting GLP-1Ra to more advanced disease, consistent with payers' restrictions but potentially not totally aligned with the mechanistic background (which would call probably for use earlier in the course of the disease). Also, it may be worth reflecting further on whether emphasis being placed on the weight loss properties of this class of drugs is leading to somewhat forgetting that the primary aim of their use should be, in line with the approved indications, improving glycaemic control, with weight loss as a highly desirable added benefit, rather than their major feature.

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Characteristics of patients with type 2 diabetes mellitus newly treated with GLP-1 receptor agonists (CHADIG Study): a cross-sectional multicentre study in Spain

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Correction

Conget I, Mauricio D, Ortega R on behalf of the CHADIG Study investigators, *et al.* Characteristics of patients with type 2 diabetes mellitus newly treated with GLP-1 receptor agonists (CHADIG Study): a cross-sectional multicentre study in Spain. *BMJ Open* 2016;**6**:e010197. doi: 10.1136/bmjopen-2015-010197

Four of the Collaborator names were written incorrectly. 'Francisco Merino Torres' should have been written 'Juan Francisco Merino-Torres', 'Fernando Gómez Peralta' as 'Fernando Gomez-Peralta', 'Diego Bellido Guerrero' as 'Diego Bellido' and 'Miguel Ángel Mangas' as 'Miguel Angel Mangas-Cruz'.

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