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Safety of SGLT2 inhibitors in very elderly diabetic type 2 patients in real life

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ABSTRACT

Introduction: Sodium glucose cotransporter 2 inhibitors (SGLT2i) are the latest antidiabetic treatments that reduces mortality and cardiovascular outcomes. Its use in real life in very elderly patients is limited by its possible side effects.

Material and methods: We conducted a retrospective study of patients treated with SGLT2i in our community (La Rioja) since 2014. The safety (adverse effects) and prognosis (mortality, cardiac decompensation, and cardiovascular events) during the first 24 months of treatment were evaluated.

Results: We included 235 patients treated with SGLT2i, 114 of them were men (48.5%), and the mean age was 79.6 ± 3.9 years. The most used SGLT2i was empagliflozin (55.7%). The mean Hb1Ac at the time of inclusion was 7.9 ± 1.4, showing a decrease in 47.7% of the included patients during the follow up. The initial values of creatinine and glomerular filtration rate at the time of inclusion (0.94 ± 0.3 and 68.3 ± 16.4) presented an improvement at 24 months of treatment (0.94 ± 0.27 and 68.2 ± 15.8). During follow-up, 94 adverse events were described in 84 patients, and 53 treatment suspensions. This adverse events were related with sex (p 0.004), dapagliflozin (p < 0.001) and initial Hb1Ac values (p 0.04). The most common adverse event were genitourinary infections (63), followed by acute kidney injury (9), being the latter the most frequent cause of treatment interruption. Symptomatic hypoglycaemia during the follow-up was related with treatment of insulin, age and Hb1Ac (p <0.01).

Conclusions: Treatment with SGLT2i is a safe and well-tolerated treatment in very elderly patients in real life. Genitourinary infections are the most common adverse events, but those that less frequently cause treatment interruption.

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Seguridad de los inhibidores de SGLT2 en pacientes diabéticos tipo 2 muy ancianos en la vida real

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RESUMEN

Introducción: Los inhibidores del cotransportador de sodio y glucosa tipo 2 (SGLT2i) son los últimos tratamientos antidiabéticos que reducen la mortalidad y los resultados cardiovasculares. Su uso en la vida real en pacientes muy ancianos está limitado por sus posibles efectos secundarios.

Material y métodos: Realizamos un estudio retrospectivo de pacientes tratados con iSGLT2 en nuestra comunidad (La Rioja) desde 2014. La seguridad (efectos adversos) y el pronóstico (mortalidad, descompensación cardiaca y eventos cardiovasculares) durante los primeros 24 meses de tratamiento fueron evaluado.

Resultados: Se incluyeron 235 pacientes tratados con SGLT2i, 114 de ellos hombres (48,5%) y la edad media fue de 79,6 ± 3,9 años. El SGLT2i más utilizado fue la empagliflozina (55,7%). La Hb1Ac media en el momento de la inclusión fue de 7,9 ± 1,4, mostrando un descenso en el 47,7% de los pacientes incluidos durante el seguimiento. Los valores iniciales de creatinina y filtrado glomerular en el momento de la inclusión (0,94 ± 0,3 y 68,3 ± 16,4) presentaron una mejoría a los 24 meses de tratamiento (0,94 ± 0,27 y 68,2 ± 15,8). Durante el seguimiento se describieron 94 eventos adversos en 84 pacientes y 53 suspensiones del tratamiento. Estos eventos adversos se relacionaron con el sexo (p 0,004), dapagliflozina (p < 0,001) y valores iniciales de Hb1Ac (p 0,04). El evento adverso más frecuente fueron las infecciones genitourinarias (63), seguidas de la insuficiencia renal aguda (9), siendo esta última la causa más frecuente de interrupción del tratamiento. La hipoglucemia sintomática durante el seguimiento se relacionó con el tratamiento de insulina, la edad y la Hb1Ac (p <0,01).

Conclusiones: El tratamiento con SGLT2i es un tratamiento seguro y bien tolerado en pacientes muy ancianos en la vida real. Las infecciones genitourinarias son los eventos adversos más frecuentes, pero los que con menor frecuencia provocan la interrupción del tratamiento.

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1. INTRODUCTION

In the United States, 21.8% of 75 years or older patients have diabetes [1]. Sodium glucose cotransporter 2 inhibitors (SGLT2i) are the latest antidiabetic treatments that reduce renal glucose reabsorption in the proximal convoluted tubule, leading to increased urinary glucose excretion [2, 3]. EMPA-REG outcome (2015), CANVAS (2017) and DECLARE-TIMI (2019) trials demonstrates the efficacy of SGLT2i in mortality and cardiovascular outcomes and determinate the safety of this pharmacological group, but include patients with a mean age less than 70 years [4-6]. We conducted this study to analyze tolerability and safety related to SGLT2i in very elderly (> 75 years) T2DM patients.

2. MATERIAL AND METHODS

We conducted a retrospective study of patients treated with SGLT2i in our community (La Rioja) since 2014. All patients older than 75 years (very elderly) were included, excluding those whose follow-up was not performed. Data was collected by the Department of Pharmacy Inspection of the community of La Rioja. Demographic information (age and sex), comorbidities (obesity, diabetes mellitus up to 10 years, target organ damage, hypertension, atrial fibrillation, heart failure, chronic kidney disease, history of cerebrovascular disease and cardiovascular disease) antidiabetic treatment [metformin, repaglinide, sulfonylurea, thiazolinediones, Dipeptidyl peptidase 4 inhibitors (DPP4i), Glucagon-like peptide-1 receptor agonists (GLP1a) and insulin] at the time of inclusion and at 24 months, the type of SGLT2i and the maximum dose were registered. To assess the tolerability of SGLT2i treatment

adverse reactions (hypoglycemia, acute kidney injury, ketoacidosis, weight loss, hypotension, urinary and genital infection) and interruption cause were recorded. Values of Hb1Ac, creatinine and glomerular filtrate performed at inclusion, 12 and 24 months were registered. To assess prognosis, mortality during follow-up, HF decompensation (hospital admission and emergency assistance) and cardiovascular diseases during 24 months before SGLT2i treatment were recorded.

all tests were two-sided, and statistical significance was set at $P < 0.05$. Statistical analysis was performed with SPSS version 22 (SPSS, Chicago, IL, USA).

3. RESULTS

Two hundred thirty-five patients treated with SGLT2i were registered. The SGLT2i used in our patients were

Table 1: Characteristic of patients and according to the SGLT2 inhibitor

	Total (n 235)	Empagliflozin (n 131)	Dapagliflozin (n 84)	Canagliflozin (n 20)
Age (years), mean ± SD	79.6 ± 3.9	79.8 ± 3.7	79.4 ± 3.9	79.5 ± 4.4
Sex, men (%)	114 (48.5%)	68 (51.9%)	37 (44%)	9 (45%)
Obesity, n (%)	104 (44.3%)	55 (42%)	39 (46.4%)	10 (50%)
Diabetes Mellitus up to 10 years, n (%)	156 (66.4%)	88 (67.2%)	53 (63.1%)	15 (75%)
Target organ damage, n (%)	49 (20.9%)	34 (26%)	13 (15.5%)	2 (10%)
Hypertension, n (%)	176 (74.9%)	98 (74.8%)	61 (72.6%)	17 (85%)
Atrial fibrillation, n (%)	61 (26%)	30 (22.9%)	27 (32.1%)	4 (20%)
Heart failure, n (%)	49 (20.9%)	25 (19.1%)	21 (25%)	3 (15%)
CKD (KDIGO stage), n (%)				
I	22 (9.4%)	12 (9.2%)	7 (8.3%)	3 (15%)
II	145 (61.5%)	86 (65.6%)	49 (58.3%)	10 (50%)
IIIA	47 (20%)	24 (18.3%)	22 (26.3%)	1 (5%)
IIIB	19 (8.1%)	9 (6.9%)	6 (7.1%)	4 (20%)
IV-V	2 (0.8%)	0	0	2 (10%)
Previous cerebrovascular disease, n (%)	22 (9.4%)	12 (9.2%)	8 (9.5%)	2 (10%)
Previous cardiovascular disease, n (%)*	56 (23.8%)	59 (30%)	14 (16.7%)	3 (15%)
Metformin, n (%)	184 (78.3%)	100 (76.3%)	68 (81%)	16 (80%)
Insulin, n (%)	52 (22.1%)	31 (23.7%)	17 (20.2%)	4 (20%)
SGLT2i suspended, n (%) [n 215]	53 (24.6%)	28 (22.8%)	21 (28.4%)	4 (21.1%)
Adverse reaction, n (%) [n 215]**	87 (40.4%)	45 (36%)	39 (52.7%)	3 (15.8%)
Mortality, n (%) [n 182]	20 (10.9%)	8 (7.8%)	11 (18%)	1 (5.9%)
Cardio/cerebro vascular diease, n (%) [n 182]	10 (5.5%)	4 (3.6%)	5 (7.9%)	1 (6.3%)
Heart failure decompensation, n (%) [n 182]	22 (12.1%)	15 (14.4%)	7 (11.1%)	0
Hb1Ac at admission (%), mean ± SD	7.9 ± 1.4	7.96 ± 1.3	8.02 ± 1.6	7.5 ± 1.3
Creatinine at admission (mg/dL), mean ± SD	0.94 ± 0.3	0.93 ± 0.25	0.94 ± 0.27	0.98 ± 0.39
Glomerular filtration rate (ml/min/1.73m^2), mean ± SD	68.3 ± 16.4	69.5 ± 15.3	67.6 ± 15.7	62.9 ± 23.8

*n: number; SD: standard deviation; 0 %: percentage; CKD: Chronic kidney disease; mg/dL: milligram per decilitre; ml: millilitre; min: minute; m2: square meter. *p < 0.05, **p <0.01.*

Normally distributed continuous variables were expressed as mean ± standard deviation (SD). If the variables were not normally distributed, median values with an interquartile range were used. Categorical variables were expressed as numbers and percentages. We analyzed normally distributed continuous variables by Student's t-test, proportions by $\chi 2$ test, and continuous variables with skewed distribution by Mann–Whitney test. The strength of the association between the outcome variable (mortality) and each variable considered was assessed by means of odds ratios (ORs) and their 95% confidence intervals (95% CIs). The P-values for

empagliflozin, in 131 (55.7%), dapagliflozin in 84 (35.7%) and canagliflozin in 20 (8.6%). The mean age was 79.6 ± 3.9 years, 114 were men (48.5%) and 104 were obese (44.3%). The most common comorbidity was hypertension, in 176 patients (74.9%), followed by diabetes mellitus up to 10 years 156 (66.4%), atrial fibrillation in 61 (26%) and heart failure in 49 (20.9%). Fifty-six patients (23.8%) had history of ischemic heart disease and 22 (9.4%) of cerebrovascular disease. Regarding antidiabetic treatment, 184 patients (78.3%) were treated with metformin, 119 (50.6%) with DDP4i, 52 (22.1%) with insulin and repaglinide, 12 (5.1%)

with sulfonylurea, 8 (3.4%) with GLP1 agonists and 2 (0.9%) with thiazolinediones. Mean Hb1Ac was 7.9 ±1.4 at the time of inclusion, 7.3 ±1 during the 12 months follow up and 7.3 ± 1.3 at the end of the follow up, showing a decrease in Hb1Ac at the end of the follow-up in 112 (47.7%) patients, with a median decrease of 0.8% (1.4-0.4). The characteristic of patients and according to the iSGLT2 used are shown in Table 1.

All patients were classified in terms of the Kidney Disease: Improving Global Outcomes (KDIGO) classification (Table 2) [7]. Twenty-two patients (9.4%) had normal renal function, 145 (61.7%) had a mild decreased (KDIGO stage 2), 47 (20%) had mild to moderate decrease (KDIGO stage 3a), 19 (8.1%) moderate to severe decrease (KDIGO stage 3b) and only 2 patients (0.8%) had a severely decreased (KDIGO stage 4). Empagliflozin was the most common SGLT2i used in stages 1 to 3b and canagliflozin is the only SGLT2i in stage 4. Albuminuria prior to the start of SLGT2i treatment had been requested in 128 patients (54.4%), being less than 30 mg/g the most common (94 patients). A worsening of initial creatinine and glomerular filtration values (0.94 ± 0.3 and 68.3 ±16.4) was observed during the first year (0.96 ± 0.27 and 66.8 ±16.7), improved at the end of follow-up (0.94 ± 0.27 and 68.2 ±15.8) not related to KDIGO stages. Twenty patients died, 22 presented heart failure decompensation, 5 had an ischemic stroke or transient ischemic attack and 5 an ischemic heart event.

and mean Hb1Ac at the time of inclusion (8 ± 1.4 vs 7.8 ± 1.3, p 0.04). Genitourinary infections were also more frequent in women (74.6%) and hypoglycemia was related to insulin treatment (10.4% vs 1.2%), age (82.7 ± 5.1 vs 79.4 ± 1.4) and Hb1Ac (9.7 ± 1.4 vs 7.9 ± 1.4) with statistical significance (p < 0.01). The most causes of treatment suspensions were acute kidney injury (8/9), while genitourinary infections (25/63) was uncommon. Six treatment interruptions were produced without adverse reactions.

4. DISCUSSION

Aging may influence the efficacy of SGLT2i due to the decrease in glomerular filtration rate and age-dependent reduction of SGLT2 expression [8]. In the main trials that study the cardiovascular benefits of SGLT2i, less than 10% of the participants were older than 75 years, even knowing that T2DM is a very frequent entity in patients of this age [9-11]. The efficacy profile and adverse reactions due to SGLT2i do not change with age, not even in elderly (> 65 years old) or very elderly patients [12]. Adverse events were lower in our study compared to those described in the literature, reaching more than 50% with canagliflozin and empagliflozin trials [10, 11]**.** Several factors influence the increase in genitourinary infections in very elderly patients,

Table 2: Patients classified according to the KDIGO classification

GFR categories (ml/min/1.73 m2)	Albuminuria			
	Not known	A1	A2	A3
		Normal/mildly increased	Moderately increased	Severely increased
		< 30 mg/g	30-300 mg/g	> 300 mg/g
G1 Normal (>90)	7 (3%)	14 (6%)	1 (0.4%)	0
G2 Mild decreased (60-89)	71 (30.2%)	49 (20.9%)	22 (9.4%)	3 (1.3%)
G3a Mild to moderate decreased (45-59)	20 (8.5%)	23 (9.8%)	4 (1.7%)	0
G3b Moderate to severe decreased (30-44)	9 (3.8%)	7 (3%)	3 (1.3%)	0
G4 Severely decreased (15-29)	0	1 (0.4%)	1 (0.4%)	0

GFR: glomerular filtration rate; mg/g: milligram per gram; ml: millilitre; min: minute; m2: square meter.

During the follow up, 94 adverse events in 84 patients were described, with 53 treatment suspensions. The most common adverse reaction was genitourinary infections (63), followed by acute kidney injury (9), symptomatic hypoglycemia (7) and hypotension (1). Other adverse reactions (14) were cachexia, urinary frequency and weight loss. Adverse reactions were related to sex (59 women vs 28 men, p 0.004), treatment with dapagliflozin (52.7% vs 36% with empagliflozin and 15.8% in canagliflozin, p < 0.001) such as menopause, urinary retention, prostatic hypertrophy, increased postvoid residual urine, urinary incontinence and increased comorbidities [13]. The most described adverse event was genitourinary infections, with a much higher frequency in our real life study compared to previous trials, but without requiring SGLT2i treatment suspension [9-11]. On the other hand, the frequency of acute kidney injury and hypoglycemia was lower, not reaching 1% in our study in contrast to previously published, probably due to the low

rate of treatment with sulfonylureas and insulin in our patients [9-11]. Most of the patients showed a glomerular filtration rate greater than 60 ml/min/1.73m2, with a slight worsening of renal function during the first year, improved after two years of treatment, similar to younger patients. The mean age of our patients and the low proportion of adverse effects and treatment suspension of SGLT2i, demonstrate the safety of this pharmacological group in very elderly patients. On the other hand, the Hb1Ac values of our patients were similar to previous trials, with a greater decrease throughout the follow-up, which demonstrates the efficacy of SGLT2i in patients older than 75 years [9-11].

In conclusion, SGLT2i treatment is effective, safe, and well tolerated in very elderly patients in real life. Despite the fact that genitourinary infections are the most frequent adverse events, they do not imply treatment interruptions.

5. CONFLICT OF INTERESTS

The authors have no conflict of interest to declare. The authors declared that this study has received no financial support.

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